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(54) Title: <b>COMPUTER-GENERATED MIMETICS WITH ENDOSTATIN COORDINATES</b>			
<div style="text-align: center;"><p>MOUSE <math>\alpha 1</math>(XVIII)</p><p>ENDOSTATIN</p><p>APLA 132 315</p><p>NC1 DOMAIN (315 aa)</p></div>			
(57) Abstract			
<p>A detailed map of atomic coordinates of active mammalian endostatin is used in a computer-based method to identify mimics having endostatin coordinates. Based on the coordinates, the computer will identify compounds having atomic coordinates with non-trivial similarity to selected coordinates of atoms of a mammalian endostatin. The method includes: a) providing a library of atomic coordinates of compounds in a library of candidate compounds; b) comparing the library atomic coordinates to the selected coordinates of a mammalian endostatin; and c) selecting from the library at least one candidate compound on the basis of selection criteria which include similarities between the atomic coordinates of the selected candidate compound and the atomic coordinates of the mammalian endostatin.</p>			

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COMPUTER-GENERATED MIMETICS WITH ENDOSTATIN COORDINATESStatement as to Federally Sponsored Research

This invention was supported in part by NIH grant  
5 AR36820, and the U.S. government has certain rights in  
the invention.

Field of the Invention

This invention is in the general field of  
computer-aided design or identification of organic  
10 compounds that mimic useful functions of known compounds.

Background of the Invention

Computers can be used to design or identify  
organic compounds that mimic the function(s) of known  
biological compounds. For example computers can be used  
15 to compare the atomic coordinates of key atoms of the  
known compounds to coordinates of atoms in known  
biological compounds.

Summary of the Invention

We have obtained a detailed map of atomic  
20 coordinates of active mammalian endostatin, and one  
preferred embodiment of the invention features computer  
generated mimics having endostatin coordinates. More  
generally, one aspect of the invention features a method  
of identifying a compound having atomic coordinates with  
25 non-trivial similarity to selected coordinates of atoms  
of a mammalian endostatin. The method includes: a)  
providing a library of atomic coordinates of compounds in  
a library of candidate compounds; b) comparing the  
library atomic coordinates to selected coordinates of a  
30 mammalian endostatin; and c) selecting from the library  
at least one candidate compound on the basis of selection  
criteria which include similarities between the atomic  
coordinates of the candidate compound and the selected  
atomic coordinates of a mammalian endostatin. We have  
35 identified certain key amino acid residues, and we  
predict that compounds (particularly non-peptides,

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meaning compounds that are not readily subject to cleavage by enzymes that cleave naturally occurring peptide bonds) having atomic coordinates close to or identical to the coordinates of the atoms in those key endostatin residues will retain important endostatin function, particularly anti-angiogenic function. Some of the key epitopes (endostatin surface areas) containing those residues are: a heparin binding epitope, residues exposed  $\alpha$ -helix A and a receptor or ligand binding epitope, which may involve an endostatin fold related to the CRD (E-selectin) oligosaccharide binding site. Other important epitopes may include those amino acids which are necessary for proteolytic cleavage. Preferably the endostatin coordinates used for selecting candidate molecules are from one or more of these surface areas (epitopes) in human endostatin. For human endostatin some of these residues are: a) Arg154, Arg157, Arg168, Arg177, Arg183, Arg192, Arg193, Arg 196, Arg258, Arg 259, and Arg 269; b) Phe161 and Phe164; and Glu266, Leu283, Ser291, His296, His297, and Tyr299. For mouse endostatin the corresponding residues are: a) Arg155, Arg158, Arg169, Arg178, Arg184, Arg 193, Arg 194, Arg197, Arg259, Arg270; b) Phe162 or Phe165; c) Glu267; Leu 284; Lys292; His297; Asn298; Tyr300. Numbering sequences given above correspond to position in NC1.

Typically the selected coordinates of endostatin atoms are stored in a computer-readable medium, and compared to coordinates of candidate compounds also stored in a computer-readable medium.

In other aspects, the invention includes anti-angiogenic fragments of endostatin comprising an epitope selected from the group consisting of a heparin binding epitope, a receptor binding epitope, an epitope exposed on  $\alpha$ -helix, and an epitope from an endostatin fold related to the CRD (E-selectin) oligosaccharide binding

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site. The invention further includes methods of treating undesired angiogenesis by administering to a patient an anti-angiogenic amount of such fragments or of a compound identified by the above method.

5                    Brief Description of the Drawings

Fig. 1 depicts the domain structure of endostatin. Triple-helical domains are indicated by rectangular boxes; non-triple-helical regions are indicated by heavy lines. The region in the COOH-terminal NC1 domain that  
10 corresponds to the proteolytic fragment endostatin is indicated. The numbering scheme is based on position in the NC1 domain as described below. The recombinant endostatin used in this work contains an APLA sequence at the NH<sub>2</sub> terminus as a result of the cloning process, which  
15 is fortuitously identical to the  $\alpha 1$ (XVIII) collagen NC1 sequence at Leu-130 and Ala-131.

Fig. 2 shows electron density maps of endostatin in the region around the  $\beta$  strand P, with the disulfide bond between Cys-164 and Cys-304 in the center. In the  
20 upper panel is the MIRAS-phased map at 2.2Å resolution after density modification. In the lower panel is the final  $2F_{\text{obs}} - F_{\text{calc}}$  map at 1.5Å resolution. Both maps are contoured at the 1.0 $\sigma$  level and are shown with the refined model superimposed. A modified version of  
25 MOLSCRIPT (Kraulis, 1991) was used.

Figs. 3A-3C show endostatin structure. Fig. 3A is a stereo C-atom trace. Spheres denote every tenth carbon atom and every 20th residue is labelled starting at Val-140. Disulfide bridges are shown with thick bands. Fig.  
30 3B is a cartoon representation, with  $\beta$  strands sequentially labelled A through P.  $\alpha$  helices are labeled. Disulfide bridges are also shown. Fig. 3C is a topology diagram. Heavy and thin diagonal lines indicate connections above and below the large  $\beta$  sheet,

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respectively. Figs. 3A and 3B were made with MOLSCRIPT (Kraulis, 1991).

Figs. 4A and 4B are electrostatic surface representation of endostatin. Dark regions indicate positive potential, and light regions indicate negative potential. The NH<sub>2</sub> and the COOH termini are indicated. Basic residues and the solvent-exposed side chains of Phe-162 and Phe-165 are labeled. The hatched areas corresponds to the oligosaccharide binding site of C-type lectin CRDs. Fig. 5A and 5B are related by a rotation of 130° about the horizontal axis. The Figs. were made by GRASP (Nicholls, 1992).

Fig. 5 (PRIOR ART) shows the nucleotide sequence of cDNA and the inferred amino acid sequence of human  $\alpha 1$ (XVIII) collagen, compared to the amino acid sequence of mouse  $\alpha 1$ (XVIII). Only residues that are different between the human and mouse sequences are shown for the mouse. Gaps

(-) or insertions (X) are shown. This figure is taken from FIG. 2 of Oh et al. *Genomics* 19:494-499 (1994).

Fig. 6 is a flow chart for performing computer-based compound selection.

Fig. 7 is a flow chart for computer-based compound design.

## 25 Description of the Preferred Embodiments

First we describe endostatin and therapies that can be developed using molecules which mimic endostatin's structure/function. Then we describe the process for designing and selecting endostatin mimics.

### 30 **Endostatin**

Endostatin is a known mammalian protein that inhibits angiogenesis, the process by which an adult mammal forms new blood vessels from existing vasculature by sprouting new capillaries. Angiogenesis is a complex

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multi-stage process involving proteolytic degradation of the basement membrane, loss of endothelial cell adhesion, proliferation and migration of endothelial cells into the surrounding stroma, and finally re-adhesion of  
5 endothelial cells to form the lumen of the new capillary tube.

Ongoing angiogenesis is thought to be essential to support the rapid growth of solid tumors, and successful tumors may actively influence angiogenesis to sustain  
10 continuous cell proliferation. Their dependence on recruiting new blood vessels from the host makes tumors vulnerable to anti-angiogenic therapy. See Hannahan and Folkman (1996).

Some of the most potent angiogenic inhibitors are  
15 fragments derived from abundant extracellular proteins that themselves do not regulate angiogenesis. One such inhibitory fragment is a 20kDa COOH-terminal fragment of collagen XVIII. This heparin binding fragment termed endostatin specifically inhibits endothelial cell  
20 proliferation and potently inhibits angiogenesis and tumor growth. O'Reilly et al. (1997). Cycled therapy with recombinant endostatin reduced several experimental tumors, including Lewis lung carcinoma, to a dormant state and did not induce resistance. Dormancy persisted  
25 after a few cycles of treatment, even when therapy was discontinued. Boehm et al. (1997).

The  $\alpha 1$ (XVIII) collagen is an unusual collagen characterized by ten domains of triple-helical collagenous repeats separated by non-triple-helical  
30 repeats (Oh et al. 1994a; Rehn and Pihlajaniemi, 1994). It is expressed in a tissue-specific manner as three alternative splice variants and is localized mainly in perivascular basement membrane zones (Muragaki et al., 1995; Rehn and Pihlajaniemi, 1995). The last six of the  
35 triple-helical repeats of  $\alpha 1$ (XVIII) collagen are almost



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identical in size to those of  $\alpha 1(XV)$  collagen (Myers et al., 1992), and the name multiplexins (for multiple triple helix domains and interruptions) has been coined for this new collagen family (Oh et al., 1994a). The  
5  $\alpha 1(XVIII)$  collagen contains a non-collagenous COOH-terminal domain (NC1) of approximately 300 residues; the angiogenic inhibitor endostatin corresponds to the last 184 amino acid residues of the NC1 domain (Figure 1). Interestingly, this exactly matches the conserved region  
10 between the 1(XVIII) of  $\alpha 1(XV)$  COOH-terminal domains (Oh et al., 1994a).

We have solved the crystal structure of endostatin at 1.5 Å resolution, enabling careful selection of organic molecules that mimic endostatin's structure and  
15 function, and thereby can inhibit undesired angiogenesis, e.g. to control cancer. Without wishing to limit ourselves to a specific molecular mechanism, we note that a large basic surface area may be the heparin binding site of endostatin, and endostatin may exert its  
20 antiproliferative effect by competing with bFGF for binding to cell surface heparin sulfate proteoglycans, which could disrupt the mitogenic growth factor signal.

#### Protein Expression and Structure Determination

Endostatin was expressed at high levels as soluble  
25 protein in human embryonic kidney cells and was found to potently inhibit the bFGF-induced proliferation of endothelial cells, with  $IC_{50}$  of about 100 ng/ml (data not shown). The secreted protein spans the 184 COOH-terminal amino acid residues of mouse  $\alpha 1(XVIII)$  collagen and  
30 additionally contains the  $NH_2$ -terminal sequence APLA (Figure 1). To avoid ambiguities caused by the  $NH_2$ -terminal splicing of  $\alpha 1(XVIII)$  collagen (Muragaki et al., 1995; Rehn and Pihlajaniemi, 1995), we decided to number



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the endostatin sequence relative to its position in the NC1 domain, starting at His-132.

The structure of endostatin was solved using crystals grown from ammonium phosphate at pH 5. Phases to 2.2 Å resolution were obtained by the multiple isomorphous replacement method and anomalous scattering (MIRAS) from three heavy atom derivatives (Table 1). The resulting electron density maps were of high quality (Figure 2A-2B), allowing the polypeptide chain to be traced without difficulty. The final structure, refined at 1.5 Å resolution, consists of residues Gln-138 to Phe-309 and a total of 83 water molecules. The first ten and last six residues are not visible and are presumed to be disordered.

#### 15 Overall Structure

Endostatin folds into a single globular domain of approximate dimensions 35 Å x 30 Å x 30 Å (Figures 3A-3C). The structure is composed predominately of β sheet and loops, but also contains two α helices, one of them short. A total of 40% of the amino acid residues adopt an extended main chain conformation, but due to many irregularities, such as kinks and bulges, only 25% are actually contained in uninterrupted β strands spanning more than two residues. The fold of endostatin is intricate and is best described with reference to a schematic representation (Fig. 3C). The most prominent feature of the structure is a highly twisted mixed β sheet composed of seven strands (E, F, A, P, J, M, O). An α helix of 14 residues, α1, packs against one face of this sheet, whereas the other face is covered by elaborate loop structures involving a short stretch of antiparallel β sheet (extends G and N) and a second shorter α helix, α2. At the COOH terminus of strand A, the polypeptide chain bulges around a water molecule before re-

35 establishing hydrogen bonding with the NH<sub>2</sub> terminus of

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strand P for another two residues. The segment following  $\alpha 1$  forms the short strand B, then kinks at Phe-180 and leads into the  $\beta$  hairpin C-D. Strands B, J and P form a triangular structure, at the center of which a water molecule hydrogen bonds with the peptide carbonyls of Phe-180 and Trp-251 and the amide nitrogen of Leu-303. This water molecule is deeply buried in the hydrophobic core and represents an integral part of the endostatin structure. Apart from the C-D  $\beta$  hairpin, there are two additional classical  $\beta$  hairpins, one extending the central  $\beta$  sheet at strand A (strands K and I), the other following strand J after a kink at Gly-253 (strands K and L). The overall arrangement of  $\beta$  strands in the endostatin structure can be described as a rather irregular  $\beta$  barrel propped open on one side by  $\alpha 2$ . Endostatin contains two disulfide bridges in a nested pattern, linking Cys-164 with Cys-304 and Cys-266 with Cys-296. The former disulfide bridge connects  $\alpha 1$  to the central  $\beta$  sheet, and the latter circularizes a twisted loop containing strands M, N and O.

Despite the disjointed fold and the large fraction of irregular loop structures, endostatin is a compact molecule. All surface loops pack tightly against the body of the structure and many of them contribute to a large hydrophobic core. This core is divided into two regions of different size by strand J. The smaller core is centered around Trp-251 and is built up mainly from amino acid side chains contributed by strands J, M, O and P. A much more extensive hydrophobic core fills the large concave face of the central  $\beta$  sheet and this is also the region where most of the longer surface loops are found.

Strands A and P of endostatin are situated next to each other, engaged in antiparallel hydrogen bonding. As a result, the first and last residue defined by the

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electron density (Gln-138 and Phe-309, respectively) are close in space. In the intact NC1 domain of collagen XVIII, endostatin is preceded by 131 residues. This NH<sub>2</sub>-terminal portion of unknown structure is likely to  
5 interact with endostatin near Phe-309 and this interaction may well lead to an ordering of the C-terminus of endostatin, which significantly contains two large hydrophobic residues, Met-310 and Phe-313. We note that the side chains of Phe-162 and Phe-165, located next  
10 to each other on  $\alpha$ 1, are fully exposed to solvent (see Fig. 4A). In the crystal lattice they are covered by a hydrophobic packing contact, and we speculate that these two residues may be involved in interdomain interactions in the full length NC1 domain.

15 Collagen XVIII is a member of the so-called multiplexin family of collagens that also includes collagen XV. These two collagens are distinguished by COOH-terminal globular domains that share 58% sequence identity in their last 184 residues corresponding to  
20 endostatin in collagen XVIII (Oh et al., 1994a). We suggest that this common region represents a new extracellular module (Bork et al., 1996), as it appears unlikely that the compact endostatin structure is a soluble fragment excised from a larger domain.

25 Interestingly, the ordered portion of the endostatin structure starts at an intro-exon boundary of  $\alpha$ 1(XVIII) collagen (Rehn et al., 1996). The autonomous folding of endostatin is also indicated by the high production rate of recombinant mouse endostatin (10-20 mg/l.d).

### 30 Comparison to Other Structures

An automated search of the DALI database (Holm and Sander, 1993; 1994) unexpectedly revealed that endostatin resembles the carbohydrate recognition domain (CRD) of mammalian C-type lectins (Weis et al., 1991; Drickamer,  
35 1993). The highest scores (Z=3.1) were obtained with E-

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selectin (Graves et al., 1994) and lithostatine, a  
homologue of the CRD that does not bind calcium or  
carbohydrate ligands (Bertrand et al., 1996). For the  
endostatin/E-selectin CRD pair, DALI identified 77  
5 equivalent residues whose C $\alpha$  atoms could be superimposed  
with an RMSD of 3.1 Å. The corresponding sequence  
identity of 9% is well below the threshold of statistical  
significance, but the high degree of structural  
similarity strongly argues for an evolutionary  
10 relationship. The entire  $\beta$  sheet structure of the E-  
selectin CRD is contained within the endostatin  
structure; only strands E and F of the central  $\beta$  sheet of  
topographically equivalent positions in the two proteins,  
but their disposition relative to the central  $\beta$  sheet  
15 varies. Significantly, both disulfide bridges in  
endostatin and E-selectin align almost perfectly when the  
three-dimensional structures are superimposed. Apart  
from Cys-296 and Cys-304, there are four additional amino  
acid residues in endostatin that have identical  
20 counterparts in the E-selectin structure. With the  
exception of the surface residue Gin-163 whose  
conservation may be adventitious, the location of these  
identities is telling: Pro-246 and Gyl-253 flank the  
crucial stand J in the large  $\beta$  sheet, and Trp-251 forms  
25 the nucleus of the smaller of the two hydrophobic cores  
in endostatin. The equivalent region in the C-type  
lectin CRD domain is the "WIGL" sequence (aromatic-  
aliphatic-glycine-aliphatic), which is the an important  
component of the C-type lectin consensus (Weis et al,  
30 1991; Drickamer, 1993).

The difference between endostatin and the E-  
selectin CRD are concentrated in two regions, situated on  
opposite faces of the central  $\beta$  sheet. In E-selectin, the  
connection between  $\alpha$ 1 and strand  $\beta$ 2 (the equivalent of  
35 endostatin  $\beta$ J) is afforded by a short strand, helix  $\alpha$ 2,

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an the loops preceding and following  $\alpha 2$ . The equivalent, much more elaborate region in endostatin contains eight, predominantly short stands (B to I) as well as  $\alpha 2$  and accounts for most of the extra residues of endostatin compared to E-selectin. In this region there is little similarity between the two structures, apart from the general location of  $\alpha 2$ . In E-selectin,  $\beta 5$  (the equivalent of endostatin  $\beta 0$ ) and the loop preceding  $\beta 4$  form a high affinity calcium binding site involved in oligosaccharide binding (Graves et al., 1994). There is no indication of calcium binding to endostatin and, indeed, we find that the long loop providing three of the five calcium ligands in E-selectin is shorter in endostatin and is arranged very differently, folded away from  $\beta 0$ .

In summary, while endostatin is doubtless related to the C-type lectin CRD, it has lost one of the defining features of this protein family, namely calcium-dependent oligosaccharide binding. This is not an unprecedented observation. We have already mentioned lithostathine, a CRD homologue that acts as an inhibitor of stone formation in the pancreas (Bertrand et al., 1996). More relevantly, the recently elucidated structure of the Link module showed that this hyaluronan binding domain resembles the C-type lectin CRD but does not use calcium for glycosaminoglycan (GAG) binding (Kohda et al., 1996). This is further discussed below in conjunction with the ligand binding properties of endostatin.

#### **A Putative Heparin Binding Site**

The mechanism(s) by which endostatin inhibits endothelial cell proliferation and angiogenesis have yet to be defined. However, given the high affinity of endostatin for heparin, interference with the heparin sulfate requirement of bFGF signalling is one possibility. Endostatin contains a large number of basic residues. In particular arginines, and their

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distribution on the protein surface provides a clue to the location of the heparin binding site. We note that of the 15 arginine residues present in mouse endostatin, all but one are fully conserved in the human protein, the  
5 exception being a conservative replacement by lysine (the overall identity between mouse and human endostatin is 87% (OH et al., 1994b). Given the genel location of arginines in surface loops, this high degree of conservation is noteworthy.

10 Falsam et al., 1996 shows two crystal structures of basic bFGF with bound heparin-derived tetra- and hexasaccharides. Basic residues may be crucial. These may be arranged as discrete clusters with a spacing that matches the distribution of GAG sulfate groups (Fromm et  
15 al., 1997). In addition, neutral polar residues may be required to provide hydrogen bonding partners for the sugar moieties (Thompson et al., 1994).

A representation of the surface electrostatic properties of endostatin is shown in Figs. 4A-4B. Eleven  
20 out of the total of 15 arginine residues cluster on one face of the molecule (Fig. 4A). This extensive basic patch (diameter = 20 Å) involves  $\alpha 1$  and  $\alpha 2$ , strand B, the long loop connecting the C-D  $\beta$  hairpin to strand E, as well as strand L and the following loop around Cys-266.  
25 The solvent-exposed side chains of Phe-162 and Phe-165 (see above) are found at the periphery of the patch. A detailed inspection highlights one particular area as a candidate heparin binding site. The two arginine pairs Arg-193/Arg-194 and Arg-259/Arg-260 form the borders of a  
30 shallow depression, at the center of which the side chain of Tyr-215 emerges, surrounded by several additional polar residues. The residues forming this putative heparin binding site are contributed by the long irregular loop preceding strand E and strand L, both  
35 elements unique to endostatin when compared to the C-type

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lectin CRD and the Link module. Binding of a larger GAG chain may involve additional arginines, possibly those centered around Arg-158.

Endostatin contains a second, less extensive basic patch roughly opposite the large area defined by the eleven arginines discussed above (Fig. 4B). This patch, composed mainly of residues contributed by the H-1  $\beta$  hairpin and the NH<sub>2</sub> terminus of strand O, is of interest because it is close to the ligand binding site in the related C-type lectins CRD (Weis et al., 1992; Grave et al., 1994). While it is conceivable that heparin may also bind to this region, we note that some of the basic residues clearly serve structural purposes and would not be available for ligand binding (Arg-230, Arg-237, and Lys-248). Furthermore, our assignment of the heparin binding site to the face bearing exclusively arginine residues (Fig. 4A) is consistent with results from chemical modification, which demonstrate the involvement in heparin binding of several arginine but no lysine residues.

The Link module, a domain of approximately 100 residues found in several extracellular matrix proteins and in the cell surface receptor CD44, is a distant relative of the C-type lectin CRD that binds the GAG hyaluronan. In the TSG-6 Link module structure (Kohda et al., 1996), a critical basic residue in the loop preceding  $\alpha$ 1 and a patch of solvent-exposed aromatic side chains define a putative hyaluronan binding site, which partly overlaps with the surface area used by the CRDs for oligosaccharide binding. In endostatin the equivalent region involves mainly strands M and O and the connecting loop to strand P, which do not coincide with either of the two basic patches described above. We therefore believe that endostatin and the Link module employs partially distinct regions for GAG binding.



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The function of the domain corresponding to endostatin in tissue-deposited collagen XVIII and XV is not known. Collagen XVIII is mainly found in vascular basement membrane regions (Muragaki et al., 1995), and  
5 the COOH-terminal NC1 domain may mediate interactions with basement membrane GAGs or proteoglycans. Full-length collagen XVIII is likely to be immobilized in some kind of network. Proteolytic cleavage in the NC1 domain, perhaps by a proteinase secreted by a tumor, could  
10 produce soluble endostatin, which would be free to diffuse to its targets and elicit its effects on endothelial cell proliferation and angiogenesis. The intact NC1 domain of collagen XVIII is not an inhibitor of angiogenesis (data not shown), corroborating earlier  
15 indications that the antiproliferative activity of endostatin may be cryptic (O'Reilly et al., 1997). It is not obvious from our structure how this regulation of activity may take place. Stearic blocking of an important epitope by the N-terminal portion of the NC1  
20 domain is a possibility. However, other scenarios can be envisaged. For instance, the exposed and mobile polypeptide chain termini of endostatin may be important for the antiproliferative effect.

Key residues of endostatin can be delineated by  
25 site-directed mutagenesis. One function of interest is heparin binding. If endostatin acts by interfering with the heparan sulfate requirement of bFGF signalling, mutations which abolish endostatin-heparin binding would be expected to be accompanied by a loss of inhibition of  
30 endothelial cell proliferation and/or angiogenesis. A second site of interest may be a site which interacts with a protein or receptor, for example of the VEGF system, causing inhibition independent of GAG binding. Heparin binding may also turn out to be only one of  
35 several critical components of the mechanism, as is the

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case with bFGF signalling. Finally, proteolytic unmasking of cryptic endostatin epitopes is a point of regulation.

#### **Experimental procedures**

##### **5 Construction of Expression Vector**

Mouse  $\alpha 1$ (XVIII) cDNA clone mc3b (Oh et al., 1994a) was used as a template to amplify the sequence encoding endostatin by polymerase chain reaction (PCR) with Vent polymerase (New England Biolabs) following the manufacturer's instructions. The primer for the 5' end was GTCAGCTAGCTCATACTCATCAGGAC and that for the 3' end was GTCACCTCGAGCTATTTGGAGAAAGAGGTC. The primers contained in addition to the annealing sequences an NheI site at the 5' end or a stop codon followed by an XhoI site at the 3' end in order to allow the in-frame insertion of the construct into the BM-40 signal peptide (Mayer et al., 1993). The PCR fragment was cloned into the modified episomal expression vector pCEP-Pu (Kohfeldt et al., 1997). The sequence of the construct was confirmed by cycle sequencing using Dye Terminator Cycle Sequencing Ready Reaction Kit (ABI).

#### **Expression and Purification of Recombinant Mouse Endostatin**

Human embryonic kidney cells that express the EBNA-1 protein from Epstein-Barr virus (293-EBNA cells, Invitrogen) were used for transfection with the expression vector (Kohfeldt et al., 1997). Resistant cells were selected with puromycin (0.5  $\mu$ g/ml) and used for collection of serum-free conditioned medium. The medium (=1 l) was dialyzed against 0.1 M NaCl, 0.05 M Tris-HCl (pH 7.4) and then applied onto a heparin-sepharose CL-6B column (2.5 x 20 cm, Pharmacia) equilibrated in the same buffer. A linear 0.1-1.0 M NaCl gradient (500 ml) was used for elution. Endostatin eluted at 0.4-0.5 M NaCl and was further purified on a

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Superose 12 column (HR16/50, Pharmacia) equilibrated in 0.2 M ammonium acetate (pH 6.8). The purified product was soluble in neutral buffer and showed a single 22 kDa band in SDS gel electrophoresis under reducing conditions. The protein has a single NH<sub>2</sub>-terminal sequence APLAHTHQ and contains less than one residue of hexosamine per molecule.

#### Crystallization and Data Collection

Crystals were obtained at room temperature by the hanging drop vapor diffusion method. Equal volumes (typically 2  $\mu$ l) of a 10 mg/ml solution of endostatin in 5 mM Tris-HCl (pH 6.,8) and 1.5-1.7 M ammonium phosphate (pH 4.7-5.3) were mixed and equilibrated against 1 ml of the latter solution. The crystals belong to space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> with unit cell constants as  $a = 45.6$  Å,  $b = 54.0$  Å,  $c = 65.9$  Å. There is one molecule of endostatin in the asymmetric unit, resulting in a solvent content of 37%. For heavy atom soaks, crystals were stabilized in 1.8 M Li<sub>2</sub>SO<sub>4</sub>, 0.1 M Na-acetate (pH 5.3). All diffraction data except native II were collected at room temperature using a MAR image plate detector mounted on a rotating anode generator operated at 4 KW (CuK $\alpha$  radiation,  $\lambda = 1.54$  Å). For derivative data collection, crystals were rotated around their carefully aligned  $a$  axis to minimize systematic errors in the measurement of Bijvoet pairs. Native II data were collected at room temperature on beamline 9.6 of the Daresbury Synchrotron Radiation Source ( $\lambda = 0.87$  Å). Data were integrated with MOSFLM (Leslie, 1994) and reduced with programs of the CCP4 suite (Collaborative Computing Project No. 4, 1994). Data collection statistics are summarized in Table 1A.

#### Structure Solution and Refinement

Three heavy atom derivatives and the native I data were used for phasing by the MIRAS method (Table 1B). Soak conditions were 3 mM UO<sub>2</sub>SO<sub>4</sub> for 3 days, 20 mM K<sub>2</sub>Pt(CN)<sub>4</sub>

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for 1 day, and 10 mM NaAu(CN)<sub>2</sub> for 2 days. Heavy atom sites were deduced from difference Patterson maps, brought to a common origin and hand by cross-phased difference Fourier maps, and refined with MLPHARE (Z. Otwinowski: Collaborative Computing project No. 4). Due to the high isomorphism of the U and Pt derivatives, useful MIRAS phases could be obtained to a resolution of 2.2 Å. The MIRAS map was subjected to density modification with DM (Cowtan and Main, 1996) in 'combine omit' mode employing solvent flattening, histogram matching and Sayre's equation. About 75% of the structure could be built with confidence into the resulting map using O (Jones et al., 1991). The remaining loop structures were added after combination of partial model phases with the experimental phases using SIGMAA (Read, 1986). The structure was first refined with X-PLOR (Brunger, 1992) against the native I data at 2.0 Å resolution to  $R_{\text{cryst}} = 0.192$  ( $R_{\text{free}} = 0.237$ ). Refinement against the synchrotron native II data was then initiated by a round of simulated annealing refinement starting from 3000 K to remove model bias, followed by conventional positional and B-factor refinement. The final model comprises residues 138 to 309 and 83 water molecules (Table 1C); 86.3% of the amino acid residues are in the most favorable regions of the Ramachandran plot, with the remaining 13.7% in additionally allowed regions, as defined by PROCHECK (Laskowski et al., 1993).

The coordinates and structural features of endostatin have been deposited in the Brookhaven Data Bank, and they are included as Appendix A to this patent application.

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Methods of Designing Mimetics

Endostatin mimetics are compounds that perform a desired endostatin function, but which are not endostatin or peptide fragments of it. Mimetics may lack some or  
5 all of the endostatin L-amino acid linking peptide bonds that characterize most mammalian proteins and peptides. In this way, mimetics may avoid rapid degradation by peptide-cleaving enzymes, thereby enhancing their in vivo lifetime.

10 Preferred mimetics will retain a key endostatin function such as inhibition of endothelial cell proliferation. They will include atoms at positions similar to those of endostatin in the key epitopes discussed above, including heparin binding, receptor  
15 binding, and epitopes controlling peptide cleavage from  $\alpha 1$ (XVIII) collagen.

The methods of the invention employ a computer-based methods for identifying compounds having a desired structure. More specifically, the invention uses the  
20 three-dimensional coordinates of a subset of the atoms in endostatin to determine peptide and non-peptide mimetic candidates by means of computer methods.

These computer-based methods fall into two broad classes: database methods and de novo design methods. In  
25 database methods the compound of interest is compared to all compounds present in a database of chemical structures and compounds whose structure is in some way similar to the compound of interest are identified. The structures in the database are based on either  
30 experimental data, generated by NMR or x-ray crystallography, or modeled three-dimensional structures based on two-dimensional (i.e., sequence) data. In de novo design methods, models of compounds whose structure is in some way similar to the compound of interest are  
35 generated by a computer program using information derived

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from known structure, e.g., data generated by x-ray crystallography and/or theoretical rules. Such design methods can build a compound having a desired structure in either an atom-by-atom manner or by assembling stored  
5 small molecular fragments.

The success of both database and de novo method in identifying compounds with activities similar to the compound of interest depends on the identification of the functionally relevant portion of the compound of  
10 interest. For drugs, the functionally relevant portion is referred to a pharmacophore. A pharmacophore then is an arrangement of structural features and functional groups important for biological activity, e.g., endostatin activity.

15 Not all identified compounds having the desired pharmacophore will act as an endostatin mimetic. The actual activity can be finally determined only by measuring the activity of the compound in relevant biological assays. However, the methods of the invention  
20 are extremely valuable because they can be used to greatly reduce the number of compounds which must be tested to identify an actual mimetic.

Programs suitable for generating predicted three-dimensional structures from two-dimensional data include:  
25 Concord (Tripos Associated, St. Louis, MO), 3-D Builder (Chemical Design Ltd., Oxford, U.K.), Catalyst (Bio-CAD Corp., Mountain View, CA), and Daylight (Abbott Laboratories, Abbott Park, IL).

Programs suitable for searching three-dimensional  
30 databases to identify molecules bearing a desired pharmacophore include: MACCS-3D and ISIS/3D (Molecular Design Ltd., San Leandro, CA), ChemDBS-3D (Chemical Design Ltd., Oxford, U.K.), and Sybyl/3DB Unity (Tripos Associates, St. Louis, MO).

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Programs suitable for pharmacophore selection and design include: DISCO (Abbott Laboratories, Abbott Park, IL), Catalyst (Bio-CAD Corp., Mountain View, CA), and ChemDBS-3D (Chemical Design Ltd., Oxford, U.K.).

5           Databases of chemical structures are available from Cambridge Crystallographic Data Center (Cambridge, U.K.) and Chemical Abstracts Service (Columbus, OH).

          De novo design programs include Ludi (Biosym Technologies Inc., San Diego, CA) and Aladdin (Daylight  
10 Chemical Information Systems, Irvine CA).

Those skilled in the art will recognize that the design of mimetic may require slight structural alteration or adjustment of a chemical structure designed or identified using the methods of the invention.

15           In general, chemical compounds identified or designed using the methods of the invention can be synthesized chemically and then tested for endostatin activity using any of the methods described below. The methods of the invention are particularly useful because  
20 they can be used to greatly decrease the number potential mimetics which must be screened for endostatin activity.

          The invention may be implemented in hardware or software, or a combination of both. However, preferably, the invention is implemented in computer programs  
25 executing on programmable computers each comprising a processor, a data storage system including volatile and non-volatile memory and/or storage elements), at least one input device, and at least one output device. Program code is applied to input data to perform the  
30 functions described above and generate output information. The output information is applied to one or more output devices, in known fashion. The computer may be, for example, a personal computer, microcomputer, or work station of conventional design.



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Each program is preferably implemented in a high level procedural or object oriented programming language to communicate with a computer system. However, the programs can be implemented in assembly or machine  
5 language, if desired. In any case, the language may be a compiled or interpreted language.

Each such computer program is preferably stored on a storage media or device (e.g., ROM or magnetic diskette) readable by a general or special purpose  
10 programmable computer, for configuring and operating the computer when the storage media or device is read by the computer to perform the procedures described herein. The inventive system may also be considered to be implemented as a computer-readable storage medium, configured with a  
15 computer program, where the storage medium so configured causes a computer to operate in a specific and predefined manner to perform the functions described herein.

Fig. 6 is a flow chart showing a first method for identifying potential mimetics using a computer system.  
20 The method uses a programmed computer comprising a processor, a data storage system, at least one input device, and at least one output device, and comprises the steps of:

- (1) inputting into the programmed computer through an  
25 input device data comprising the three-dimensional coordinates of a subset of the atoms in endostatin, thereby generating a criteria data set (STEP 100);
- (2) comparing, using the processor, the criteria data  
30 set to a computer database of chemical structures stored in the computer data storage system (STEP 102);
- (3) selecting from the database, using a program  
35 suitable for searching three-dimensional databases to identify molecules bearing a desired

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pharmacophore (such as those described above or equivalents), chemical structures having a portion that is structurally similar to the criteria data set (STEP 104);

- 5 (4) outputting to an output device the selected chemical structures having a portion similar to the criteria data set (STEP 106).

Fig. 7 is a flow chart showing a second method for identifying potential mimetics of endostatin using a  
10 computer system. The method uses a programmed computer comprising a processor, a data storage system, at least one input device, and at least one output device, and comprises the steps of:

- (1) inputting into the programmed computer through an  
15 input device data comprising the three-dimensional coordinates of a atoms of endostatin, thereby generating a criteria data set (STEP 200);
- (2) constructing, using a program suitable for generating chemical structure models (such as  
20 those described above or equivalents), a model of a chemical structure having a portion that is structurally similar to the criteria data set (STEP 202);
- (3) outputting to the output device the constructed  
25 model (STEP 204).

#### Confirmation of Biological Activity

In order to determine whether a molecule identified using the methods of the invention can act as an endostatin mimetic, one or more *in vitro* or *in vivo*  
30 assays of endostatin activity should be performed. For example, mimetic molecules should be able to inhibit endothelial cell proliferation in the following assay using human umbilical vein endothelial cells (HUVEC's) or human arterila endothelial cells (HAEC's).

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Gelatin-coated multi-well plates are prepared by incubating 0.3ml of attachment factor solution (Cascade Biologic, Inc., Portland OR) for 30 min. at 37°C or for 2 hrs. at room temperature. The attachment factor solution is aspirated. A suspension of  $2.5 \times 10^4$  cells/ml of HUVEC in M200 (Cascade Biologic) supplemented with Low Serum Growth Supplement (LSGS, also from Cascade Biologic) is prepared. 0.5ml of the suspension is added to each well, and the cells are incubated at 37°C and 5%CO<sub>2</sub> for 24hrs.

10 The medium is then replaced with sample test solutions (e.g., with concentrations ranging from 0-500ng/ml) prepared from sample stock solutions by dilution with M200 supplemented with LSGS. 0.5ml of sample test solution is added to each well and incubated  
15 at 37°C and 5%CO<sub>2</sub> for 48hrs.

An MMT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrasolium bromide) assay is performed to determine cell proliferation. MMT is dissolved to 5mg/ml in PBS and filtered (0.2µm). 50µl of MMT solution is added to each  
20 well for the last 4 hours of the 48hr incubation. Medium is aspirated. 0.4ml of isopropanol with 0.04N HCl is added to each well and absorbance is measured at 570nm. Decreased absorbance relative to control indicates inhibition of proliferation.

25 Using assays based on the above procedures, we have determined that several endostatin-containing fragments inhibit endothelial cell proliferation at a level comparable to human endostatin. For example, human NC1-N-terminal segment, human NC1-C-terminal segment, and  
30 mouse endostatin fragments inhibit endothelial cell proliferation.

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**PROVISIONAL APPLICATION**

**UNDER 37 CFR 1.53(b)(2)**

**APPENDIX A**

**TITLE:                   COMPUTER-GENERATED MIMETICS WITH ENDOSTATIN  
COORDINATES**

**APPLICANT:           BJORN R. OLSEN  
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REMA

REMA crystal structure of mouse endostatin at 1.5 A resolution

REMA authors: E Hohenester, T Sasaki, BR Olsen, and R Timpl

REMA

CRYST1 45.560 53.950 65.850 90.00 90.00 90.00

ATOM	1	CB	GLN	138	16.060	38.907	58.366	1.00	10.71
ATOM	2	CG	GLN	138	15.910	39.108	56.861	1.00	11.99
ATOM	3	CD	GLN	138	14.462	39.216	56.438	1.00	17.23
ATOM	4	OE1	GLN	138	13.740	40.078	56.909	1.00	19.56
ATOM	5	NE2	GLN	138	14.020	38.315	55.565	1.00	19.22
ATOM	6	C	GLN	138	16.020	36.457	58.023	1.00	16.16
ATOM	7	O	GLN	138	17.226	36.330	57.871	1.00	16.26
ATOM	8	N	GLN	138	15.825	37.355	60.311	1.00	19.63
ATOM	9	CA	GLN	138	15.467	37.593	58.873	1.00	15.07
ATOM	10	N	PRO	139	15.146	35.591	57.498	1.00	15.25
ATOM	11	CD	PRO	139	13.687	35.481	57.641	1.00	15.29
ATOM	12	CA	PRO	139	15.679	34.496	56.678	1.00	12.81
ATOM	13	CB	PRO	139	14.453	33.619	56.444	1.00	13.97
ATOM	14	CG	PRO	139	13.327	34.567	56.473	1.00	19.89
ATOM	15	C	PRO	139	16.271	34.987	55.379	1.00	9.18
ATOM	16	O	PRO	139	15.816	35.984	54.818	1.00	11.04
ATOM	17	N	VAL	140	17.301	34.287	54.921	1.00	10.21
ATOM	18	CA	VAL	140	17.960	34.598	53.657	1.00	9.99
ATOM	19	CB	VAL	140	19.204	35.503	53.854	1.00	10.45
ATOM	20	CG1	VAL	140	18.813	36.882	54.376	1.00	10.92
ATOM	21	CG2	VAL	140	20.197	34.833	54.753	1.00	9.04
ATOM	22	C	VAL	140	18.458	33.277	53.077	1.00	11.74
ATOM	23	O	VAL	140	18.630	32.309	53.809	1.00	13.00
ATOM	24	N	LEU	141	18.697	33.256	51.768	1.00	10.15
ATOM	25	CA	LEU	141	19.251	32.096	51.073	1.00	9.08
ATOM	26	CB	LEU	141	18.272	31.542	50.033	1.00	10.41
ATOM	27	CG	LEU	141	16.952	30.968	50.545	1.00	12.91
ATOM	28	CD1	LEU	141	16.125	30.494	49.349	1.00	13.77
ATOM	29	CD2	LEU	141	17.215	29.825	51.518	1.00	10.92
ATOM	30	C	LEU	141	20.495	32.597	50.355	1.00	8.62
ATOM	31	O	LEU	141	20.434	33.581	49.600	1.00	9.84
ATOM	32	N	HIS	142	21.622	31.931	50.575	1.00	6.26
ATOM	33	CA	HIS	142	22.871	32.331	49.933	1.00	7.37
ATOM	34	CB	HIS	142	24.070	31.977	50.812	1.00	6.13
ATOM	35	CG	HIS	142	24.093	32.703	52.125	1.00	9.30
ATOM	36	CD2	HIS	142	24.697	33.863	52.491	1.00	11.21
ATOM	37	ND1	HIS	142	23.408	32.261	53.232	1.00	10.67
ATOM	38	CE1	HIS	142	23.583	33.115	54.229	1.00	11.23
ATOM	39	NE2	HIS	142	24.360	34.089	53.807	1.00	9.19
ATOM	40	C	HIS	142	23.078	31.728	48.521	1.00	9.63

ATOM	41	O	HIS	142	22.824	30.530	48.298	1.00	8.50
ATOM	42	N	LEU	143	23.531	32.561	47.587	1.00	5.90
ATOM	43	CA	LEU	143	23.840	32.138	46.217	1.00	6.16
ATOM	44	CB	LEU	143	23.086	32.994	45.199	1.00	7.80
ATOM	45	CG	LEU	143	23.227	32.617	43.721	1.00	8.59
ATOM	46	CD1	LEU	143	22.603	31.276	43.438	1.00	8.94
ATOM	47	CD2	LEU	143	22.540	33.694	42.866	1.00	11.98
ATOM	48	C	LEU	143	25.355	32.363	46.123	1.00	8.08
ATOM	49	O	LEU	143	25.829	33.492	46.235	1.00	8.41
ATOM	50	N	VAL	144	26.116	31.289	45.927	1.00	7.00
ATOM	51	CA	VAL	144	27.570	31.337	45.956	1.00	6.28
ATOM	52	CB	VAL	144	28.077	30.721	47.303	1.00	7.09
ATOM	53	CG1	VAL	144	29.576	30.910	47.456	1.00	9.37
ATOM	54	CG2	VAL	144	27.352	31.358	48.494	1.00	10.88
ATOM	55	C	VAL	144	28.175	30.546	44.806	1.00	7.86
ATOM	56	O	VAL	144	27.695	29.470	44.461	1.00	8.99
ATOM	57	N	ALA	145	29.231	31.075	44.207	1.00	7.05
ATOM	58	CA	ALA	145	29.870	30.388	43.092	1.00	8.14
ATOM	59	CB	ALA	145	30.501	31.423	42.154	1.00	8.87
ATOM	60	C	ALA	145	30.938	29.359	43.511	1.00	8.47
ATOM	61	O	ALA	145	31.633	29.530	44.538	1.00	8.37
ATOM	62	N	LEU	146	31.071	28.302	42.709	1.00	7.30
ATOM	63	CA	LEU	146	32.131	27.326	42.934	1.00	8.01
ATOM	64	CB	LEU	146	32.013	26.134	41.982	1.00	6.67
ATOM	65	CG	LEU	146	30.862	25.161	42.280	1.00	9.61
ATOM	66	CD1	LEU	146	30.912	24.036	41.268	1.00	9.50
ATOM	67	CD2	LEU	146	31.010	24.558	43.693	1.00	11.47
ATOM	68	C	LEU	146	33.478	28.051	42.732	1.00	7.11
ATOM	69	O	LEU	146	33.572	29.018	41.964	1.00	9.42
ATOM	70	N	ASN	147	34.523	27.552	43.376	1.00	6.40
ATOM	71	CA	ASN	147	35.832	28.192	43.333	1.00	7.10
ATOM	72	CB	ASN	147	36.705	27.692	44.489	1.00	7.91
ATOM	73	CG	ASN	147	36.176	28.129	45.853	1.00	8.97
ATOM	74	OD1	ASN	147	35.563	29.189	45.993	1.00	11.21
ATOM	75	ND2	ASN	147	36.423	27.309	46.870	1.00	10.82
ATOM	76	C	ASN	147	36.591	28.134	42.011	1.00	9.58
ATOM	77	O	ASN	147	37.658	28.738	41.896	1.00	10.63
ATOM	78	N	THR	148	36.098	27.348	41.058	1.00	7.40
ATOM	79	CA	THR	148	36.722	27.297	39.738	1.00	9.45
ATOM	80	CB	THR	148	37.623	26.049	39.514	1.00	13.02
ATOM	81	OG1	THR	148	36.799	24.881	39.398	1.00	17.83
ATOM	82	CG2	THR	148	38.619	25.862	40.643	1.00	15.46
ATOM	83	C	THR	148	35.616	27.168	38.713	1.00	9.36
ATOM	84	O	THR	148	34.503	26.758	39.042	1.00	8.96
ATOM	85	N	PRO	149	35.877	27.637	37.473	1.00	12.03
ATOM	86	CD	PRO	149	37.022	28.417	36.982	1.00	16.15
ATOM	87	CA	PRO	149	34.849	27.500	36.441	1.00	10.16
ATOM	88	CB	PRO	149	35.412	28.335	35.287	1.00	12.46
ATOM	89	CG	PRO	149	36.883	28.269	35.478	1.00	15.97
ATOM	90	C	PRO	149	34.840	26.015	36.092	1.00	9.92
ATOM	91	O	PRO	149	35.786	25.280	36.438	1.00	12.33
ATOM	92	N	LEU	150	33.777	25.569	35.431	1.00	9.68
ATOM	93	CA	LEU	150	33.653	24.181	35.020	1.00	8.42

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ATOM	94	CB	LEU	150	32.665	23.451	35.933	1.00	11.10
ATOM	95	CG	LEU	150	33.047	23.170	37.403	1.00	13.54
ATOM	96	CD1	LEU	150	31.913	22.375	38.058	1.00	15.50
ATOM	97	CD2	LEU	150	34.336	22.387	37.477	1.00	14.35
ATOM	98	C	LEU	150	33.114	24.130	33.610	1.00	7.98
ATOM	99	O	LEU	150	32.371	25.015	33.190	1.00	8.15
ATOM	100	N	SER	151	33.521	23.116	32.862	1.00	9.42
ATOM	101	CA	SER	151	32.987	22.923	31.515	1.00	9.11
ATOM	102	CB	SER	151	33.938	22.048	30.692	1.00	10.20
ATOM	103	OG	SER	151	33.940	20.711	31.169	1.00	10.67
ATOM	104	C	SER	151	31.657	22.175	31.729	1.00	9.32
ATOM	105	O	SER	151	31.269	21.901	32.866	1.00	10.06
ATOM	106	N	GLY	152	30.984	21.809	30.644	1.00	7.94
ATOM	107	CA	GLY	152	29.736	21.087	30.761	1.00	8.69
ATOM	108	C	GLY	152	29.902	19.660	31.274	1.00	9.35
ATOM	109	O	GLY	152	28.917	19.036	31.659	1.00	11.59
ATOM	110	N	GLY	153	31.126	19.127	31.230	1.00	8.17
ATOM	111	CA	GLY	153	31.381	17.774	31.719	1.00	10.98
ATOM	112	C	GLY	153	31.692	17.856	33.202	1.00	10.16
ATOM	113	O	GLY	153	32.860	17.943	33.591	1.00	11.38
ATOM	114	N	MET	154	30.642	17.821	34.027	1.00	10.00
ATOM	115	CA	MET	154	30.768	17.957	35.488	1.00	9.58
ATOM	116	CB	MET	154	29.716	18.945	35.997	1.00	9.96
ATOM	117	CG	MET	154	29.738	20.301	35.324	1.00	12.59
ATOM	118	SD	MET	154	28.413	21.305	35.982	1.00	14.27
ATOM	119	CE	MET	154	28.373	22.677	34.791	1.00	16.15
ATOM	120	C	MET	154	30.553	16.668	36.256	1.00	11.76
ATOM	121	O	MET	154	30.429	16.701	37.484	1.00	9.48
ATOM	122	N	ARG	155	30.520	15.551	35.531	1.00	12.28
ATOM	123	CA	ARG	155	30.250	14.226	36.102	1.00	11.91
ATOM	124	CB	ARG	155	31.163	13.908	37.289	1.00	11.17
ATOM	125	CG	ARG	155	32.637	13.800	36.905	1.00	17.34
ATOM	126	CD	ARG	155	33.464	13.057	37.966	1.00	21.82
ATOM	127	NE	ARG	155	33.823	13.921	39.084	1.00	36.87
ATOM	128	CZ	ARG	155	34.692	14.924	39.004	0.00	30.58
ATOM	129	NH1	ARG	155	35.307	15.197	37.854	0.00	29.77
ATOM	130	NH2	ARG	155	34.911	15.687	40.066	0.00	29.77
ATOM	131	C	ARG	155	28.784	14.188	36.516	1.00	12.08
ATOM	132	O	ARG	155	28.404	13.550	37.513	1.00	12.85
ATOM	133	N	GLY	156	27.958	14.870	35.725	1.00	8.74
ATOM	134	CA	GLY	156	26.539	14.929	35.972	1.00	7.52
ATOM	135	C	GLY	156	26.163	15.848	37.120	1.00	7.97
ATOM	136	O	GLY	156	27.025	16.469	37.746	1.00	8.74
ATOM	137	N	ILE	157	24.868	15.894	37.421	1.00	9.58
ATOM	138	CA	ILE	157	24.382	16.725	38.498	1.00	8.21
ATOM	139	CB	ILE	157	22.849	16.831	38.459	1.00	12.87
ATOM	140	CG2	ILE	157	22.212	15.495	38.838	1.00	14.12
ATOM	141	CG1	ILE	157	22.388	17.998	39.353	1.00	13.81
ATOM	142	CD1	ILE	157	22.782	19.366	38.796	1.00	13.09
ATOM	143	C	ILE	157	24.906	16.218	39.862	1.00	8.75
ATOM	144	O	ILE	157	25.107	17.011	40.771	1.00	7.94
ATOM	145	N	ARG	158	25.123	14.905	40.011	1.00	8.52
ATOM	146	CA	ARG	158	25.670	14.382	41.272	1.00	8.29



ATOM	147	CB	ARG	158	25.735	12.841	41.263	1.00	9.85
ATOM	148	CG	ARG	158	24.374	12.165	41.245	1.00	13.49
ATOM	149	CD	ARG	158	24.497	10.663	41.084	1.00	12.24
ATOM	150	NE	ARG	158	23.220	10.010	41.373	1.00	15.33
ATOM	151	CZ	ARG	158	22.969	8.710	41.187	1.00	15.84
ATOM	152	NH1	ARG	158	23.917	7.910	40.708	1.00	14.08
ATOM	153	NH2	ARG	158	21.770	8.214	41.490	1.00	17.98
ATOM	154	C	ARG	158	27.075	14.973	41.488	1.00	8.10
ATOM	155	O	ARG	158	27.445	15.301	42.616	1.00	10.27
ATOM	156	N	GLY	159	27.832	15.147	40.397	1.00	8.31
ATOM	157	CA	GLY	159	29.172	15.709	40.472	1.00	7.59
ATOM	158	C	GLY	159	29.130	17.171	40.900	1.00	10.13
ATOM	159	O	GLY	159	29.836	17.592	41.819	1.00	9.79
ATOM	160	N	ALA	160	28.276	17.946	40.240	1.00	9.09
ATOM	161	CA	ALA	160	28.119	19.371	40.547	1.00	8.50
ATOM	162	CB	ALA	160	27.173	20.028	39.550	1.00	10.08
ATOM	163	C	ALA	160	27.606	19.567	41.976	1.00	7.04
ATOM	164	O	ALA	160	28.133	20.388	42.727	1.00	8.57
ATOM	165	N	ASP	161	26.583	18.812	42.352	1.00	6.23
ATOM	166	CA	ASP	161	26.034	18.902	43.708	1.00	6.78
ATOM	167	CB	ASP	161	24.830	17.955	43.883	1.00	9.35
ATOM	168	CG	ASP	161	23.504	18.553	43.386	1.00	11.70
ATOM	169	OD1	ASP	161	23.458	19.756	43.070	1.00	9.81
ATOM	170	OD2	ASP	161	22.484	17.814	43.340	1.00	11.63
ATOM	171	C	ASP	161	27.092	18.546	44.752	1.00	7.76
ATOM	172	O	ASP	161	27.152	19.161	45.818	1.00	8.73
ATOM	173	N	PHE	162	27.939	17.558	44.459	1.00	7.42
ATOM	174	CA	PHE	162	28.979	17.169	45.409	1.00	6.73
ATOM	175	CB	PHE	162	29.656	15.869	44.963	1.00	7.02
ATOM	176	CG	PHE	162	30.679	15.369	45.929	1.00	9.17
ATOM	177	CD1	PHE	162	30.384	15.275	47.285	1.00	11.91
ATOM	178	CD2	PHE	162	31.931	14.981	45.490	1.00	17.16
ATOM	179	CE1	PHE	162	31.340	14.787	48.203	1.00	16.73
ATOM	180	CE2	PHE	162	32.888	14.495	46.391	1.00	22.21
ATOM	181	CZ	PHE	162	32.591	14.399	47.746	1.00	14.81
ATOM	182	C	PHE	162	30.014	18.309	45.573	1.00	9.46
ATOM	183	O	PHE	162	30.534	18.548	46.671	1.00	9.44
ATOM	184	N	GLN	163	30.336	19.000	44.477	1.00	8.27
ATOM	185	CA	GLN	163	31.272	20.124	44.549	1.00	7.65
ATOM	186	CB	GLN	163	31.576	20.667	43.151	1.00	9.20
ATOM	187	CG	GLN	163	32.539	19.790	42.365	1.00	18.91
ATOM	188	CD	GLN	163	33.857	19.587	43.107	1.00	39.76
ATOM	189	OE1	GLN	163	34.541	20.556	43.459	1.00	52.67
ATOM	190	NE2	GLN	163	34.201	18.326	43.385	1.00	48.77
ATOM	191	C	GLN	163	30.694	21.215	45.464	1.00	7.86
ATOM	192	O	GLN	163	31.414	21.754	46.307	1.00	9.18
ATOM	193	N	CYS	164	29.409	21.535	45.295	1.00	5.94
ATOM	194	CA	CYS	164	28.751	22.532	46.142	1.00	5.67
ATOM	195	C	CYS	164	28.836	22.113	47.619	1.00	8.49
ATOM	196	O	CYS	164	29.109	22.938	48.498	1.00	11.21
ATOM	197	CB	CYS	164	27.283	22.704	45.742	1.00	7.87
ATOM	198	SG	CYS	164	27.037	23.568	44.153	1.00	8.48
ATOM	199	N	PHE	165	28.589	20.834	47.880	1.00	8.20

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ATOM	200	CA	PHE	165	28.648	20.279	49.237	1.00	9.36
ATOM	201	CB	PHE	165	28.264	18.786	49.206	1.00	7.82
ATOM	202	CG	PHE	165	28.450	18.079	50.530	1.00	7.97
ATOM	203	CD1	PHE	165	27.409	18.024	51.458	1.00	12.10
ATOM	204	CD2	PHE	165	29.665	17.482	50.851	1.00	14.48
ATOM	205	CE1	PHE	165	27.587	17.380	52.699	1.00	12.63
ATOM	206	CE2	PHE	165	29.847	16.842	52.084	1.00	17.07
ATOM	207	CZ	PHE	165	28.806	16.798	52.997	1.00	10.01
ATOM	208	C	PHE	165	30.052	20.435	49.828	1.00	9.82
ATOM	209	O	PHE	165	30.228	20.953	50.939	1.00	7.80
ATOM	210	N	GLN	166	31.056	19.987	49.079	1.00	7.84
ATOM	211	CA	GLN	166	32.436	20.052	49.536	1.00	9.67
ATOM	212	CB	GLN	166	33.367	19.386	48.523	1.00	10.91
ATOM	213	CG	GLN	166	33.330	17.887	48.588	1.00	18.10
ATOM	214	CD	GLN	166	33.824	17.357	49.945	1.00	34.87
ATOM	215	OE1	GLN	166	34.965	16.907	50.058	1.00	42.81
ATOM	216	NE2	GLN	166	32.972	17.419	50.974	1.00	32.60
ATOM	217	C	GLN	166	32.928	21.468	49.803	1.00	11.38
ATOM	218	O	GLN	166	33.501	21.756	50.868	1.00	11.23
ATOM	219	N	GLN	167	32.670	22.368	48.862	1.00	9.13
ATOM	220	CA	GLN	167	33.154	23.727	49.007	1.00	8.13
ATOM	221	CB	GLN	167	33.158	24.409	47.651	1.00	8.05
ATOM	222	CG	GLN	167	34.112	23.695	46.726	1.00	11.07
ATOM	223	CD	GLN	167	34.234	24.338	45.357	1.00	12.90
ATOM	224	OE1	GLN	167	33.986	25.533	45.199	1.00	10.57
ATOM	225	NE2	GLN	167	34.645	23.552	44.364	1.00	12.82
ATOM	226	C	GLN	167	32.479	24.543	50.094	1.00	8.77
ATOM	227	O	GLN	167	33.132	25.365	50.754	1.00	9.77
ATOM	228	N	ALA	168	31.202	24.274	50.335	1.00	7.44
ATOM	229	CA	ALA	168	30.475	24.976	51.404	1.00	8.42
ATOM	230	CB	ALA	168	28.964	24.700	51.304	1.00	9.12
ATOM	231	C	ALA	168	31.010	24.509	52.773	1.00	9.57
ATOM	232	O	ALA	168	31.233	25.310	53.683	1.00	11.46
ATOM	233	N	ARG	169	31.219	23.203	52.890	1.00	9.90
ATOM	234	CA	ARG	169	31.711	22.578	54.106	1.00	11.80
ATOM	235	CB	ARG	169	31.753	21.064	53.880	1.00	15.49
ATOM	236	CG	ARG	169	32.049	20.219	55.079	1.00	37.27
ATOM	237	CD	ARG	169	32.180	18.759	54.671	1.00	52.08
ATOM	238	NE	ARG	169	31.918	17.856	55.791	1.00	65.31
ATOM	239	CZ	ARG	169	30.697	17.580	56.255	1.00	73.82
ATOM	240	NH1	ARG	169	29.625	18.141	55.690	1.00	74.58
ATOM	241	NH2	ARG	169	30.543	16.755	57.292	1.00	77.05
ATOM	242	C	ARG	169	33.107	23.096	54.457	1.00	12.57
ATOM	243	O	ARG	169	33.404	23.346	55.629	1.00	12.02
ATOM	244	N	ALA	170	33.943	23.291	53.437	1.00	10.85
ATOM	245	CA	ALA	170	35.316	23.755	53.619	1.00	10.67
ATOM	246	CB	ALA	170	36.058	23.765	52.286	1.00	8.66
ATOM	247	C	ALA	170	35.392	25.132	54.264	1.00	11.92
ATOM	248	O	ALA	170	36.365	25.441	54.943	1.00	14.09
ATOM	249	N	VAL	171	34.375	25.964	54.046	1.00	10.84
ATOM	250	CA	VAL	171	34.365	27.308	54.621	1.00	10.43
ATOM	251	CB	VAL	171	34.126	28.399	53.543	1.00	11.31
ATOM	252	CG1	VAL	171	35.245	28.335	52.525	1.00	14.10

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ATOM	253	CG2 VAL	171	32.773	28.225	52.852	1.00	11.12
ATOM	254	C VAL	171	33.424	27.471	55.797	1.00	10.80
ATOM	255	O VAL	171	33.055	28.579	56.167	1.00	12.10
ATOM	256	N GLY	172	32.977	26.356	56.340	1.00	12.04
ATOM	257	CA GLY	172	32.131	26.429	57.511	1.00	13.35
ATOM	258	C GLY	172	30.699	26.875	57.342	1.00	15.12
ATOM	259	O GLY	172	30.073	27.285	58.318	1.00	15.40
ATOM	260	N LEU	173	30.168	26.818	56.125	1.00	13.41
ATOM	261	CA LEU	173	28.768	27.183	55.909	1.00	15.44
ATOM	262	CB LEU	173	28.519	27.534	54.455	1.00	14.81
ATOM	263	CG LEU	173	29.272	28.782	53.997	1.00	19.11
ATOM	264	CD1 LEU	173	28.947	29.080	52.537	1.00	20.09
ATOM	265	CD2 LEU	173	28.899	29.978	54.883	1.00	24.38
ATOM	266	C LEU	173	27.925	25.985	56.307	1.00	21.13
ATOM	267	O LEU	173	28.253	24.851	55.961	1.00	24.24
ATOM	268	N SER	174	26.839	26.231	57.033	1.00	26.10
ATOM	269	CA SER	174	25.980	25.152	57.527	1.00	28.96
ATOM	270	CB SER	174	25.478	25.501	58.935	1.00	34.55
ATOM	271	OG SER	174	26.566	25.731	59.820	1.00	47.56
ATOM	272	C SER	174	24.793	24.721	56.667	1.00	28.64
ATOM	273	O SER	174	24.275	23.611	56.833	1.00	33.02
ATOM	274	N GLY	175	24.331	25.593	55.785	1.00	21.73
ATOM	275	CA GLY	175	23.188	25.223	54.975	1.00	23.45
ATOM	276	C GLY	175	23.441	24.121	53.963	1.00	22.56
ATOM	277	O GLY	175	24.584	23.685	53.761	1.00	23.28
ATOM	278	N THR	176	22.360	23.691	53.315	1.00	19.93
ATOM	279	CA THR	176	22.409	22.665	52.280	1.00	18.67
ATOM	280	CB THR	176	21.163	21.749	52.340	1.00	27.39
ATOM	281	OG1 THR	176	21.035	21.204	53.665	1.00	33.04
ATOM	282	CG2 THR	176	21.293	20.599	51.329	1.00	29.21
ATOM	283	C THR	176	22.468	23.362	50.914	1.00	13.33
ATOM	284	O THR	176	21.508	23.988	50.481	1.00	15.59
ATOM	285	N PHE	177	23.611	23.254	50.254	1.00	11.56
ATOM	286	CA PHE	177	23.816	23.881	48.954	1.00	10.99
ATOM	287	CB PHE	177	25.181	24.551	48.911	1.00	9.82
ATOM	288	CG PHE	177	25.273	25.774	49.774	1.00	13.27
ATOM	289	CD1 PHE	177	25.489	25.656	51.147	1.00	11.48
ATOM	290	CD2 PHE	177	25.140	27.042	49.218	1.00	11.67
ATOM	291	CE1 PHE	177	25.572	26.782	51.948	1.00	13.02
ATOM	292	CE2 PHE	177	25.226	28.170	50.021	1.00	15.24
ATOM	293	CZ PHE	177	25.442	28.037	51.386	1.00	12.92
ATOM	294	C PHE	177	23.727	22.897	47.811	1.00	12.80
ATOM	295	O PHE	177	24.366	21.842	47.845	1.00	14.50
ATOM	296	N ARG	178	22.945	23.258	46.803	1.00	8.14
ATOM	297	CA ARG	178	22.790	22.438	45.617	1.00	9.25
ATOM	298	CB ARG	178	21.344	21.949	45.519	1.00	15.01
ATOM	299	CG ARG	178	20.983	20.981	46.652	1.00	22.66
ATOM	300	CD ARG	178	19.910	19.993	46.265	1.00	28.20
ATOM	301	NE ARG	178	20.264	19.281	45.043	1.00	30.10
ATOM	302	CZ ARG	178	19.399	18.961	44.086	1.00	30.96
ATOM	303	NH1 ARG	178	18.113	19.293	44.219	1.00	25.66
ATOM	304	NH2 ARG	178	19.823	18.340	42.983	1.00	28.72
ATOM	305	C ARG	178	23.204	23.257	44.386	1.00	9.34

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ATOM	306	O	ARG	178	23.174	24.488	44.418	1.00	8.16
ATOM	307	N	ALA	179	23.657	22.589	43.329	1.00	7.60
ATOM	308	CA	ALA	179	24.069	23.290	42.117	1.00	6.68
ATOM	309	CB	ALA	179	24.734	22.320	41.146	1.00	7.71
ATOM	310	C	ALA	179	22.871	23.972	41.465	1.00	7.17
ATOM	311	O	ALA	179	21.780	23.405	41.399	1.00	8.52
ATOM	312	N	PHE	180	23.092	25.211	41.021	1.00	6.55
ATOM	313	CA	PHE	180	22.102	26.061	40.349	1.00	8.23
ATOM	314	CB	PHE	180	22.610	27.523	40.456	1.00	7.58
ATOM	315	CG	PHE	180	21.645	28.583	39.950	1.00	7.95
ATOM	316	CD1	PHE	180	20.580	29.029	40.743	1.00	10.05
ATOM	317	CD2	PHE	180	21.839	29.173	38.705	1.00	10.04
ATOM	318	CE1	PHE	180	19.726	30.065	40.304	1.00	13.92
ATOM	319	CE2	PHE	180	20.998	30.204	38.262	1.00	12.57
ATOM	320	CZ	PHE	180	19.940	30.650	39.070	1.00	10.87
ATOM	321	C	PHE	180	22.040	25.592	38.873	1.00	7.43
ATOM	322	O	PHE	180	22.592	26.229	37.981	1.00	8.61
ATOM	323	N	LEU	181	21.404	24.452	38.630	1.00	7.22
ATOM	324	CA	LEU	181	21.333	23.894	37.285	1.00	6.87
ATOM	325	CB	LEU	181	22.520	22.923	37.065	1.00	8.00
ATOM	326	CG	LEU	181	23.990	23.348	37.182	1.00	6.24
ATOM	327	CD1	LEU	181	24.918	22.140	37.255	1.00	6.93
ATOM	328	CD2	LEU	181	24.347	24.231	35.999	1.00	9.85
ATOM	329	C	LEU	181	20.083	23.039	37.145	1.00	9.21
ATOM	330	O	LEU	181	19.619	22.465	38.133	1.00	9.14
ATOM	331	N	SER	182	19.506	22.993	35.941	1.00	7.07
ATOM	332	CA	SER	182	18.403	22.062	35.686	1.00	7.88
ATOM	333	CB	SER	182	17.500	22.550	34.551	1.00	8.40
ATOM	334	OG	SER	182	16.552	23.491	35.006	1.00	8.46
ATOM	335	C	SER	182	19.114	20.774	35.226	1.00	10.02
ATOM	336	O	SER	182	20.248	20.825	34.737	1.00	11.73
ATOM	337	N	SER	183	18.476	19.623	35.390	1.00	9.61
ATOM	338	CA	SER	183	19.070	18.365	34.937	1.00	10.74
ATOM	339	CB	SER	183	19.908	17.707	36.044	1.00	16.99
ATOM	340	OG	SER	183	19.155	17.500	37.243	1.00	22.50
ATOM	341	C	SER	183	17.933	17.458	34.462	1.00	10.89
ATOM	342	O	SER	183	16.777	17.857	34.491	1.00	10.38
ATOM	343	N	ARG	184	18.257	16.243	34.033	1.00	13.32
ATOM	344	CA	ARG	184	17.235	15.336	33.520	1.00	13.60
ATOM	345	CB	ARG	184	17.844	13.957	33.217	1.00	21.11
ATOM	346	CG	ARG	184	16.818	12.903	32.776	1.00	31.07
ATOM	347	CD	ARG	184	17.484	11.718	32.074	1.00	51.84
ATOM	348	NE	ARG	184	18.168	12.133	30.839	1.00	75.25
ATOM	349	CZ	ARG	184	17.571	12.370	29.663	1.00	83.77
ATOM	350	NH1	ARG	184	16.250	12.227	29.524	1.00	84.96
ATOM	351	NH2	ARG	184	18.293	12.812	28.633	1.00	85.63
ATOM	352	C	ARG	184	15.969	15.175	34.356	1.00	12.92
ATOM	353	O	ARG	184	14.867	15.231	33.822	1.00	16.34
ATOM	354	N	LEU	185	16.125	14.990	35.663	1.00	12.43
ATOM	355	CA	LEU	185	14.984	14.788	36.550	1.00	15.55
ATOM	356	CB	LEU	185	15.285	13.613	37.466	1.00	17.61
ATOM	357	CG	LEU	185	15.577	12.307	36.755	1.00	22.06
ATOM	358	CD1	LEU	185	16.091	11.332	37.798	1.00	23.60

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ATOM	359	CD2 LEU	185	14.308	11.791	36.064	1.00	23.85
ATOM	360	C LEU	185	14.647	15.979	37.439	1.00	15.27
ATOM	361	O LEU	185	13.753	15.900	38.280	1.00	17.36
ATOM	362	N GLN	186	15.258	17.119	37.182	1.00	12.21
ATOM	363	CA GLN	186	15.048	18.245	38.060	1.00	13.64
ATOM	364	CB GLN	186	16.195	18.224	39.090	1.00	22.75
ATOM	365	CG GLN	186	16.299	19.426	39.993	1.00	37.49
ATOM	366	CD GLN	186	15.537	19.254	41.288	1.00	46.69
ATOM	367	OE1 GLN	186	16.072	18.714	42.266	1.00	52.06
ATOM	368	NE2 GLN	186	14.304	19.761	41.331	1.00	48.85
ATOM	369	C GLN	186	15.033	19.599	37.369	1.00	11.79
ATOM	370	O GLN	186	15.936	19.909	36.610	1.00	14.24
ATOM	371	N ASP	187	13.988	20.379	37.606	1.00	10.45
ATOM	372	CA ASP	187	13.926	21.736	37.076	1.00	10.04
ATOM	373	CB ASP	187	12.486	22.228	36.988	1.00	13.26
ATOM	374	CG ASP	187	11.684	21.479	35.970	1.00	15.08
ATOM	375	OD1 ASP	187	12.185	21.293	34.844	1.00	14.31
ATOM	376	OD2 ASP	187	10.555	21.063	36.287	1.00	21.37
ATOM	377	C ASP	187	14.640	22.598	38.120	1.00	10.87
ATOM	378	O ASP	187	14.478	22.398	39.326	1.00	11.85
ATOM	379	N LEU	188	15.442	23.544	37.664	1.00	10.75
ATOM	380	CA LEU	188	16.157	24.450	38.559	1.00	8.93
ATOM	381	CB LEU	188	16.853	25.524	37.723	1.00	9.42
ATOM	382	CG LEU	188	17.432	26.782	38.380	1.00	11.08
ATOM	383	CD1 LEU	188	18.419	26.387	39.464	1.00	14.34
ATOM	384	CD2 LEU	188	18.133	27.607	37.298	1.00	13.25
ATOM	385	C LEU	188	15.177	25.122	39.538	1.00	10.07
ATOM	386	O LEU	188	15.459	25.248	40.731	1.00	10.11
ATOM	387	N TYR	189	14.009	25.506	39.037	1.00	8.69
ATOM	388	CA TYR	189	13.022	26.183	39.878	1.00	10.49
ATOM	389	CB TYR	189	11.753	26.502	39.075	1.00	10.54
ATOM	390	CG TYR	189	10.717	27.195	39.926	1.00	17.51
ATOM	391	CD1 TYR	189	10.844	28.552	40.265	1.00	17.16
ATOM	392	CE1 TYR	189	9.911	29.177	41.105	1.00	17.25
ATOM	393	CD2 TYR	189	9.628	26.484	40.438	1.00	19.22
ATOM	394	CE2 TYR	189	8.700	27.097	41.274	1.00	21.20
ATOM	395	CZ TYR	189	8.847	28.436	41.604	1.00	20.23
ATOM	396	OH TYR	189	7.917	28.986	42.442	1.00	17.62
ATOM	397	C TYR	189	12.648	25.454	41.171	1.00	11.00
ATOM	398	O TYR	189	12.494	26.073	42.227	1.00	11.72
ATOM	399	N SER	190	12.554	24.133	41.090	1.00	10.73
ATOM	400	CA SER	190	12.150	23.295	42.213	1.00	9.77
ATOM	401	CB SER	190	11.622	21.972	41.674	1.00	13.82
ATOM	402	OG SER	190	10.448	22.187	40.921	1.00	28.12
ATOM	403	C SER	190	13.176	22.975	43.261	1.00	10.02
ATOM	404	O SER	190	12.835	22.339	44.259	1.00	12.81
ATOM	405	N ILE	191	14.421	23.395	43.054	1.00	10.13
ATOM	406	CA ILE	191	15.517	23.102	43.982	1.00	11.69
ATOM	407	CB ILE	191	16.877	23.514	43.386	1.00	12.50
ATOM	408	CG2 ILE	191	17.960	23.455	44.434	1.00	22.45
ATOM	409	CG1 ILE	191	17.239	22.597	42.223	1.00	14.35
ATOM	410	CD1 ILE	191	18.549	22.986	41.579	1.00	19.08
ATOM	411	C ILE	191	15.353	23.726	45.373	1.00	16.53



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ATOM	412	O	ILE	191	15.811	23.147	46.364	1.00	17.93
ATOM	413	N	VAL	192	14.756	24.916	45.436	1.00	14.25
ATOM	414	CA	VAL	192	14.513	25.599	46.708	1.00	13.18
ATOM	415	CB	VAL	192	14.528	27.142	46.515	1.00	10.04
ATOM	416	CG1	VAL	192	13.966	27.853	47.745	1.00	11.77
ATOM	417	CG2	VAL	192	15.965	27.603	46.235	1.00	11.81
ATOM	418	C	VAL	192	13.168	25.137	47.280	1.00	13.46
ATOM	419	O	VAL	192	12.185	25.069	46.546	1.00	14.59
ATOM	420	N	ARG	193	13.150	24.777	48.567	1.00	15.32
ATOM	421	CA	ARG	193	11.933	24.305	49.256	1.00	15.89
ATOM	422	CB	ARG	193	12.159	24.211	50.775	1.00	20.17
ATOM	423	CG	ARG	193	13.164	23.153	51.232	0.00	17.65
ATOM	424	CD	ARG	193	12.731	21.734	50.874	0.00	16.70
ATOM	425	NE	ARG	193	13.064	21.385	49.496	0.00	15.78
ATOM	426	CZ	ARG	193	14.272	20.998	49.093	0.00	15.27
ATOM	427	NH1	ARG	193	15.276	20.901	49.960	0.00	15.06
ATOM	428	NH2	ARG	193	14.477	20.727	47.815	0.00	15.06
ATOM	429	C	ARG	193	10.784	25.248	48.983	1.00	17.12
ATOM	430	O	ARG	193	10.948	26.470	49.038	1.00	16.17
ATOM	431	N	ARG	194	9.609	24.678	48.732	1.00	17.83
ATOM	432	CA	ARG	194	8.419	25.468	48.408	1.00	19.92
ATOM	433	CB	ARG	194	7.180	24.560	48.282	1.00	21.81
ATOM	434	CG	ARG	194	5.877	25.289	48.014	0.00	19.23
ATOM	435	CD	ARG	194	4.722	24.309	47.932	0.00	17.77
ATOM	436	NE	ARG	194	3.438	24.985	47.772	0.00	16.39
ATOM	437	CZ	ARG	194	2.317	24.382	47.384	0.00	15.52
ATOM	438	NH1	ARG	194	2.316	23.080	47.111	0.00	15.16
ATOM	439	NH2	ARG	194	1.193	25.079	47.280	0.00	15.16
ATOM	440	C	ARG	194	8.145	26.620	49.377	1.00	19.00
ATOM	441	O	ARG	194	7.823	27.734	48.951	1.00	18.27
ATOM	442	N	ALA	195	8.308	26.361	50.671	1.00	18.54
ATOM	443	CA	ALA	195	8.059	27.384	51.675	1.00	18.53
ATOM	444	CB	ALA	195	8.064	26.765	53.048	1.00	20.42
ATOM	445	C	ALA	195	9.016	28.576	51.630	1.00	19.26
ATOM	446	O	ALA	195	8.679	29.659	52.117	1.00	21.44
ATOM	447	N	ASP	196	10.171	28.404	50.998	1.00	15.48
ATOM	448	CA	ASP	196	11.154	29.473	50.929	1.00	14.34
ATOM	449	CB	ASP	196	12.541	28.927	51.279	1.00	14.53
ATOM	450	CG	ASP	196	12.634	28.446	52.714	1.00	25.06
ATOM	451	OD1	ASP	196	11.932	29.008	53.577	1.00	31.54
ATOM	452	OD2	ASP	196	13.390	27.497	52.979	1.00	23.54
ATOM	453	C	ASP	196	11.230	30.158	49.585	1.00	13.66
ATOM	454	O	ASP	196	12.082	31.008	49.385	1.00	16.79
ATOM	455	N	ARG	197	10.314	29.849	48.678	1.00	13.68
ATOM	456	CA	ARG	197	10.359	30.429	47.340	1.00	12.56
ATOM	457	CB	ARG	197	9.655	29.505	46.353	1.00	11.95
ATOM	458	CG	ARG	197	10.266	28.145	46.232	1.00	11.67
ATOM	459	CD	ARG	197	9.529	27.313	45.206	1.00	16.62
ATOM	460	NE	ARG	197	10.017	25.945	45.257	1.00	19.60
ATOM	461	CZ	ARG	197	9.342	24.878	44.843	1.00	21.25
ATOM	462	NH1	ARG	197	8.123	25.013	44.336	1.00	22.10
ATOM	463	NH2	ARG	197	9.901	23.672	44.918	1.00	19.31
ATOM	464	C	ARG	197	9.785	31.824	47.152	1.00	14.21

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ATOM	465	O	ARG	197	10.253	32.574	46.308	1.00	12.84
ATOM	466	N	GLY	198	8.812	32.200	47.968	1.00	16.37
ATOM	467	CA	GLY	198	8.174	33.474	47.737	1.00	15.07
ATOM	468	C	GLY	198	8.604	34.693	48.499	1.00	17.12
ATOM	469	O	GLY	198	8.419	35.796	48.007	1.00	21.05
ATOM	470	N	SER	199	9.217	34.543	49.655	1.00	17.39
ATOM	471	CA	SER	199	9.544	35.745	50.377	1.00	20.73
ATOM	472	CB	SER	199	8.390	36.084	51.313	1.00	28.27
ATOM	473	OG	SER	199	8.143	34.981	52.162	1.00	37.53
ATOM	474	C	SER	199	10.831	35.719	51.146	1.00	20.82
ATOM	475	O	SER	199	10.973	36.435	52.137	1.00	22.75
ATOM	476	N	VAL	200	11.770	34.888	50.716	1.00	16.33
ATOM	477	CA	VAL	200	13.058	34.837	51.383	1.00	13.69
ATOM	478	CB	VAL	200	13.466	33.388	51.750	1.00	13.63
ATOM	479	CG1	VAL	200	14.843	33.377	52.360	1.00	11.91
ATOM	480	CG2	VAL	200	12.471	32.792	52.752	1.00	15.70
ATOM	481	C	VAL	200	14.090	35.490	50.441	1.00	12.91
ATOM	482	O	VAL	200	14.311	35.020	49.328	1.00	11.93
ATOM	483	N	PRO	201	14.680	36.623	50.847	1.00	10.78
ATOM	484	CD	PRO	201	14.477	37.430	52.062	1.00	9.78
ATOM	485	CA	PRO	201	15.655	37.246	49.959	1.00	11.08
ATOM	486	CB	PRO	201	16.067	38.511	50.723	1.00	11.01
ATOM	487	CG	PRO	201	15.763	38.210	52.136	1.00	16.40
ATOM	488	C	PRO	201	16.851	36.376	49.606	1.00	9.78
ATOM	489	O	PRO	201	17.291	35.556	50.404	1.00	10.76
ATOM	490	N	ILE	202	17.348	36.549	48.387	1.00	9.72
ATOM	491	CA	ILE	202	18.528	35.831	47.913	1.00	11.47
ATOM	492	CB	ILE	202	18.423	35.467	46.407	1.00	12.59
ATOM	493	CG2	ILE	202	19.674	34.695	45.956	1.00	10.13
ATOM	494	CG1	ILE	202	17.118	34.681	46.131	1.00	12.81
ATOM	495	CD1	ILE	202	16.991	33.329	46.828	1.00	12.75
ATOM	496	C	ILE	202	19.690	36.800	48.099	1.00	9.90
ATOM	497	O	ILE	202	19.632	37.939	47.633	1.00	9.51
ATOM	498	N	VAL	203	20.743	36.345	48.770	1.00	8.31
ATOM	499	CA	VAL	203	21.907	37.184	49.053	1.00	8.59
ATOM	500	CB	VAL	203	22.029	37.520	50.603	1.00	9.06
ATOM	501	CG1	VAL	203	20.739	38.145	51.114	1.00	9.64
ATOM	502	CG2	VAL	203	22.381	36.272	51.424	1.00	10.29
ATOM	503	C	VAL	203	23.184	36.488	48.628	1.00	8.32
ATOM	504	O	VAL	203	23.194	35.274	48.402	1.00	9.94
ATOM	505	N	ASN	204	24.246	37.260	48.462	1.00	7.22
ATOM	506	CA	ASN	204	25.530	36.669	48.126	1.00	6.18
ATOM	507	CB	ASN	204	26.384	37.605	47.253	1.00	7.17
ATOM	508	CG	ASN	204	26.786	38.882	47.957	1.00	10.87
ATOM	509	OD1	ASN	204	26.814	38.957	49.189	1.00	10.05
ATOM	510	ND2	ASN	204	27.170	39.877	47.172	1.00	11.25
ATOM	511	C	ASN	204	26.246	36.210	49.419	1.00	7.48
ATOM	512	O	ASN	204	25.678	36.301	50.517	1.00	8.60
ATOM	513	N	LEU	205	27.477	35.722	49.284	1.00	8.24
ATOM	514	CA	LEU	205	28.260	35.223	50.406	1.00	10.00
ATOM	515	CB	LEU	205	29.650	34.835	49.911	1.00	11.80
ATOM	516	CG	LEU	205	30.610	34.229	50.944	1.00	13.04
ATOM	517	CD1	LEU	205	30.155	32.829	51.290	1.00	19.40



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ATOM	518	CD2 LEU	205	32.037	34.215	50.398	1.00	14.64
ATOM	519	C LEU	205	28.387	36.242	51.543	1.00	12.19
ATOM	520	O LEU	205	28.441	35.864	52.716	1.00	13.21
ATOM	521	N LYS	206	28.481	37.519	51.175	1.00	10.81
ATOM	522	CA LYS	206	28.623	38.622	52.127	1.00	13.25
ATOM	523	CB LYS	206	29.507	39.717	51.528	1.00	13.08
ATOM	524	CG LYS	206	30.959	39.260	51.291	1.00	23.58
ATOM	525	CD LYS	206	31.813	40.348	50.659	1.00	35.02
ATOM	526	CE LYS	206	33.304	40.035	50.793	1.00	46.91
ATOM	527	NZ LYS	206	33.658	38.654	50.333	1.00	57.40
ATOM	528	C LYS	206	27.285	39.209	52.582	1.00	15.01
ATOM	529	O LYS	206	27.246	40.297	53.166	1.00	14.89
ATOM	530	N ASP	207	26.204	38.476	52.339	1.00	10.24
ATOM	531	CA ASP	207	24.858	38.886	52.720	1.00	10.26
ATOM	532	CB ASP	207	24.701	39.036	54.251	1.00	10.80
ATOM	533	CG ASP	207	24.771	37.710	54.988	1.00	16.79
ATOM	534	OD1 ASP	207	24.694	36.645	54.362	1.00	16.98
ATOM	535	OD2 ASP	207	24.896	37.720	56.222	1.00	19.23
ATOM	536	C ASP	207	24.309	40.113	52.011	1.00	11.53
ATOM	537	O ASP	207	23.379	40.748	52.505	1.00	14.87
ATOM	538	N GLU	208	24.880	40.461	50.864	1.00	9.33
ATOM	539	CA GLU	208	24.374	41.586	50.078	1.00	9.28
ATOM	540	CB GLU	208	25.459	42.094	49.144	1.00	10.70
ATOM	541	CG GLU	208	26.664	42.535	49.953	1.00	13.38
ATOM	542	CD GLU	208	27.861	42.970	49.142	1.00	22.15
ATOM	543	OE1 GLU	208	28.047	42.537	47.967	1.00	15.62
ATOM	544	OE2 GLU	208	28.648	43.754	49.722	1.00	27.12
ATOM	545	C GLU	208	23.177	41.063	49.301	1.00	11.06
ATOM	546	O GLU	208	23.246	39.999	48.658	1.00	10.86
ATOM	547	N VAL	209	22.063	41.779	49.394	1.00	9.59
ATOM	548	CA VAL	209	20.829	41.352	48.756	1.00	10.86
ATOM	549	CB VAL	209	19.620	42.141	49.290	1.00	11.29
ATOM	550	CG1 VAL	209	18.313	41.594	48.704	1.00	11.00
ATOM	551	CG2 VAL	209	19.607	42.087	50.813	1.00	11.82
ATOM	552	C VAL	209	20.887	41.425	47.251	1.00	13.44
ATOM	553	O VAL	209	21.249	42.465	46.687	1.00	14.37
ATOM	554	N LEU	210	20.555	40.302	46.610	1.00	10.99
ATOM	555	CA LEU	210	20.567	40.180	45.143	1.00	11.77
ATOM	556	CB LEU	210	21.245	38.868	44.717	1.00	10.60
ATOM	557	CG LEU	210	22.655	38.615	45.248	1.00	11.69
ATOM	558	CD1 LEU	210	23.111	37.258	44.788	1.00	15.27
ATOM	559	CD2 LEU	210	23.621	39.672	44.783	1.00	15.32
ATOM	560	C LEU	210	19.174	40.221	44.541	1.00	11.30
ATOM	561	O LEU	210	18.970	40.777	43.469	1.00	13.41
ATOM	562	N SER	211	18.218	39.620	45.230	1.00	12.59
ATOM	563	CA SER	211	16.843	39.560	44.748	1.00	12.51
ATOM	564	CB SER	211	16.700	38.362	43.783	1.00	12.81
ATOM	565	OG SER	211	15.363	38.168	43.380	1.00	17.30
ATOM	566	C SER	211	15.924	39.402	45.962	1.00	12.70
ATOM	567	O SER	211	16.319	38.822	46.978	1.00	13.12
ATOM	568	N PRO	212	14.701	39.966	45.890	1.00	12.25
ATOM	569	CD PRO	212	14.207	40.842	44.810	1.00	13.48
ATOM	570	CA PRO	212	13.734	39.876	46.995	1.00	12.35

ATOM	571	CB	PRO	212	12.603	40.813	46.544	1.00	14.48
ATOM	572	CG	PRO	212	12.730	40.829	45.043	1.00	13.98
ATOM	573	C	PRO	212	13.230	38.466	47.303	1.00	11.21
ATOM	574	O	PRO	212	12.808	38.179	48.430	1.00	13.32
ATOM	575	N	SER	213	13.322	37.575	46.322	1.00	10.85
ATOM	576	CA	SER	213	12.877	36.199	46.494	1.00	9.69
ATOM	577	CB	SER	213	11.347	36.119	46.500	1.00	12.14
ATOM	578	OG	SER	213	10.833	36.434	45.216	1.00	12.73
ATOM	579	C	SER	213	13.373	35.340	45.347	1.00	10.77
ATOM	580	O	SER	213	13.870	35.834	44.334	1.00	11.42
ATOM	581	N	TRP	214	13.201	34.039	45.516	1.00	11.69
ATOM	582	CA	TRP	214	13.573	33.052	44.512	1.00	11.56
ATOM	583	CB	TRP	214	13.429	31.661	45.138	1.00	12.36
ATOM	584	CG	TRP	214	13.706	30.501	44.220	1.00	11.79
ATOM	585	CD2	TRP	214	14.992	30.059	43.744	1.00	10.04
ATOM	586	CE2	TRP	214	14.784	28.837	43.053	1.00	10.39
ATOM	587	CE3	TRP	214	16.299	30.572	43.844	1.00	9.25
ATOM	588	CD1	TRP	214	12.798	29.570	43.782	1.00	12.27
ATOM	589	NE1	TRP	214	13.437	28.571	43.089	1.00	10.10
ATOM	590	CZ2	TRP	214	15.839	28.115	42.460	1.00	9.77
ATOM	591	CZ3	TRP	214	17.347	29.861	43.255	1.00	10.46
ATOM	592	CH2	TRP	214	17.108	28.638	42.572	1.00	10.11
ATOM	593	C	TRP	214	12.629	33.202	43.317	1.00	10.01
ATOM	594	O	TRP	214	13.063	33.291	42.172	1.00	11.47
ATOM	595	N	ASP	215	11.335	33.305	43.601	1.00	10.89
ATOM	596	CA	ASP	215	10.323	33.438	42.557	1.00	11.93
ATOM	597	CB	ASP	215	8.926	33.600	43.165	1.00	12.37
ATOM	598	CG	ASP	215	8.324	32.292	43.599	1.00	21.53
ATOM	599	OD1	ASP	215	8.934	31.235	43.333	1.00	21.13
ATOM	600	OD2	ASP	215	7.234	32.330	44.212	1.00	25.53
ATOM	601	C	ASP	215	10.583	34.601	41.629	1.00	11.83
ATOM	602	O	ASP	215	10.324	34.512	40.433	1.00	14.03
ATOM	603	N	SER	216	11.074	35.703	42.179	1.00	12.12
ATOM	604	CA	SER	216	11.343	36.893	41.375	1.00	15.57
ATOM	605	CB	SER	216	11.925	38.008	42.250	1.00	17.98
ATOM	606	OG	SER	216	11.019	38.315	43.287	1.00	37.82
ATOM	607	C	SER	216	12.284	36.624	40.217	1.00	13.80
ATOM	608	O	SER	216	12.184	37.253	39.164	1.00	16.51
ATOM	609	N	LEU	217	13.204	35.687	40.405	1.00	13.84
ATOM	610	CA	LEU	217	14.159	35.361	39.349	1.00	16.15
ATOM	611	CB	LEU	217	15.291	34.483	39.905	1.00	13.80
ATOM	612	CG	LEU	217	16.230	35.009	40.991	1.00	16.30
ATOM	613	CD1	LEU	217	17.166	33.873	41.400	1.00	18.85
ATOM	614	CD2	LEU	217	17.033	36.196	40.491	1.00	19.33
ATOM	615	C	LEU	217	13.518	34.633	38.162	1.00	15.00
ATOM	616	O	LEU	217	13.995	34.730	37.028	1.00	15.72
ATOM	617	N	PHE	218	12.422	33.931	38.427	1.00	14.28
ATOM	618	CA	PHE	218	11.764	33.113	37.411	1.00	15.74
ATOM	619	CB	PHE	218	11.556	31.698	37.989	1.00	12.34
ATOM	620	CG	PHE	218	12.820	31.081	38.495	1.00	12.47
ATOM	621	CD1	PHE	218	13.152	31.151	39.853	1.00	12.13
ATOM	622	CD2	PHE	218	13.715	30.476	37.607	1.00	11.71
ATOM	623	CE1	PHE	218	14.353	30.645	40.317	1.00	12.68

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ATOM	624	CE2 PHE	218	14.934	29.959	38.064	1.00	12.62
ATOM	625	CZ PHE	218	15.260	30.044	39.427	1.00	11.54
ATOM	626	C PHE	218	10.462	33.673	36.872	1.00	19.66
ATOM	627	O PHE	218	9.680	32.961	36.240	1.00	19.44
ATOM	628	N SER	219	10.291	34.979	37.037	1.00	20.96
ATOM	629	CA SER	219	9.092	35.704	36.612	1.00	20.25
ATOM	630	CB SER	219	9.107	37.069	37.285	1.00	18.96
ATOM	631	OG SER	219	10.301	37.740	36.904	1.00	24.95
ATOM	632	C SER	219	9.013	35.941	35.103	1.00	19.87
ATOM	633	O SER	219	7.959	36.318	34.565	1.00	20.23
ATOM	634	N GLY	220	10.151	35.817	34.439	1.00	16.90
ATOM	635	CA GLY	220	10.200	36.063	33.015	1.00	18.69
ATOM	636	C GLY	220	11.197	37.177	32.734	1.00	19.82
ATOM	637	O GLY	220	11.512	37.439	31.586	1.00	22.45
ATOM	638	N SER	221	11.718	37.801	33.791	1.00	20.73
ATOM	639	CA SER	221	12.703	38.891	33.692	1.00	20.97
ATOM	640	CB SER	221	12.840	39.571	35.057	1.00	18.70
ATOM	641	OG SER	221	13.371	38.657	36.017	1.00	29.42
ATOM	642	C SER	221	14.084	38.349	33.294	1.00	20.66
ATOM	643	O SER	221	15.019	39.120	33.039	1.00	19.09
ATOM	644	N GLN	222	14.212	37.022	33.324	1.00	15.11
ATOM	645	CA GLN	222	15.450	36.314	33.011	1.00	14.71
ATOM	646	CB GLN	222	16.056	36.757	31.663	1.00	16.07
ATOM	647	CG GLN	222	15.106	36.574	30.479	1.00	23.55
ATOM	648	CD GLN	222	15.802	36.549	29.147	1.00	27.05
ATOM	649	OE1 GLN	222	16.784	37.258	28.932	1.00	39.97
ATOM	650	NE2 GLN	222	15.289	35.742	28.229	1.00	34.40
ATOM	651	C GLN	222	16.479	36.423	34.142	1.00	13.28
ATOM	652	O GLN	222	17.682	36.457	33.883	1.00	13.22
ATOM	653	N GLY	223	15.993	36.452	35.390	1.00	12.76
ATOM	654	CA GLY	223	16.862	36.522	36.562	1.00	11.74
ATOM	655	C GLY	223	17.691	37.782	36.642	1.00	12.55
ATOM	656	O GLY	223	18.902	37.746	36.884	1.00	10.85
ATOM	657	N GLN	224	17.025	38.906	36.408	1.00	15.41
ATOM	658	CA GLN	224	17.656	40.215	36.425	1.00	18.36
ATOM	659	CB GLN	224	16.651	41.251	35.899	1.00	24.28
ATOM	660	CG GLN	224	17.165	42.686	35.786	1.00	30.95
ATOM	661	CD GLN	224	18.211	42.865	34.703	1.00	37.18
ATOM	662	OE1 GLN	224	19.411	42.959	34.987	1.00	41.40
ATOM	663	NE2 GLN	224	17.764	42.923	33.451	1.00	34.95
ATOM	664	C GLN	224	18.137	40.593	37.826	1.00	19.75
ATOM	665	O GLN	224	17.386	40.504	38.802	1.00	23.25
ATOM	666	N LEU	225	19.408	40.945	37.939	1.00	18.83
ATOM	667	CA LEU	225	19.937	41.357	39.226	1.00	23.64
ATOM	668	CB LEU	225	21.302	40.733	39.510	1.00	23.44
ATOM	669	CG LEU	225	21.418	39.204	39.546	1.00	21.44
ATOM	670	CD1 LEU	225	22.849	38.826	39.846	1.00	30.04
ATOM	671	CD2 LEU	225	20.493	38.586	40.573	1.00	23.51
ATOM	672	C LEU	225	20.052	42.864	39.183	1.00	26.18
ATOM	673	O LEU	225	20.007	43.469	38.120	1.00	27.58
ATOM	674	N GLN	226	20.094	43.482	40.349	1.00	33.02
ATOM	675	CA GLN	226	20.221	44.928	40.404	1.00	35.26
ATOM	676	CB GLN	226	19.951	45.420	41.819	1.00	41.02

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ATOM	677	CG	GLN	226	19.221	46.746	41.863	1.00	50.30
ATOM	678	CD	GLN	226	19.298	47.404	43.206	1.00	62.18
ATOM	679	OE1	GLN	226	18.313	47.447	43.936	1.00	69.77
ATOM	680	NE2	GLN	226	20.469	47.930	43.545	1.00	63.73
ATOM	681	C	GLN	226	21.644	45.287	39.995	1.00	34.91
ATOM	682	O	GLN	226	22.581	44.522	40.253	1.00	34.64
ATOM	683	N	PRO	227	21.830	46.456	39.363	1.00	36.79
ATOM	684	CD	PRO	227	20.802	47.459	39.025	1.00	40.94
ATOM	685	CA	PRO	227	23.154	46.907	38.924	1.00	36.81
ATOM	686	CB	PRO	227	22.898	48.354	38.471	1.00	38.12
ATOM	687	CG	PRO	227	21.510	48.295	37.973	1.00	42.81
ATOM	688	C	PRO	227	24.144	46.871	40.080	1.00	34.94
ATOM	689	O	PRO	227	23.774	47.111	41.235	1.00	32.98
ATOM	690	N	GLY	228	25.389	46.538	39.768	1.00	32.98
ATOM	691	CA	GLY	228	26.408	46.504	40.796	1.00	30.54
ATOM	692	C	GLY	228	26.394	45.263	41.658	1.00	28.50
ATOM	693	O	GLY	228	27.285	45.110	42.497	1.00	30.52
ATOM	694	N	ALA	229	25.384	44.404	41.486	1.00	25.56
ATOM	695	CA	ALA	229	25.276	43.143	42.241	1.00	22.10
ATOM	696	CB	ALA	229	24.112	42.296	41.705	1.00	21.32
ATOM	697	C	ALA	229	26.581	42.383	42.058	1.00	18.87
ATOM	698	O	ALA	229	27.128	42.367	40.964	1.00	21.82
ATOM	699	N	ARG	230	27.092	41.799	43.134	1.00	16.13
ATOM	700	CA	ARG	230	28.345	41.035	43.113	1.00	14.81
ATOM	701	CB	ARG	230	29.321	41.571	44.160	1.00	14.64
ATOM	702	CG	ARG	230	29.824	42.937	43.902	1.00	26.70
ATOM	703	CD	ARG	230	30.941	43.241	44.854	1.00	26.86
ATOM	704	NE	ARG	230	30.510	43.360	46.248	1.00	27.65
ATOM	705	CZ	ARG	230	31.318	43.782	47.219	1.00	34.32
ATOM	706	NH1	ARG	230	32.573	44.110	46.922	1.00	31.38
ATOM	707	NH2	ARG	230	30.897	43.862	48.475	1.00	28.97
ATOM	708	C	ARG	230	28.087	39.581	43.493	1.00	12.29
ATOM	709	O	ARG	230	27.240	39.292	44.346	1.00	13.37
ATOM	710	N	ILE	231	28.824	38.675	42.871	1.00	9.91
ATOM	711	CA	ILE	231	28.706	37.271	43.217	1.00	10.26
ATOM	712	CB	ILE	231	28.123	36.417	42.071	1.00	13.89
ATOM	713	CG2	ILE	231	28.197	34.914	42.441	1.00	13.66
ATOM	714	CG1	ILE	231	26.676	36.869	41.796	1.00	16.94
ATOM	715	CD1	ILE	231	25.967	36.091	40.731	1.00	20.65
ATOM	716	C	ILE	231	30.091	36.795	43.600	1.00	9.79
ATOM	717	O	ILE	231	31.062	37.018	42.874	1.00	10.47
ATOM	718	N	PHE	232	30.188	36.265	44.813	1.00	10.02
ATOM	719	CA	PHE	232	31.443	35.739	45.358	1.00	10.35
ATOM	720	CB	PHE	232	31.621	36.196	46.818	1.00	8.78
ATOM	721	CG	PHE	232	31.751	37.672	46.970	1.00	11.12
ATOM	722	CD1	PHE	232	30.638	38.464	47.202	1.00	12.05
ATOM	723	CD2	PHE	232	32.989	38.278	46.863	1.00	16.49
ATOM	724	CE1	PHE	232	30.763	39.839	47.316	1.00	19.05
ATOM	725	CE2	PHE	232	33.116	39.668	46.978	1.00	16.99
ATOM	726	CZ	PHE	232	32.008	40.438	47.201	1.00	13.69
ATOM	727	C	PHE	232	31.478	34.204	45.350	1.00	10.13
ATOM	728	O	PHE	232	30.439	33.544	45.496	1.00	9.50
ATOM	729	N	SER	233	32.680	33.658	45.186	1.00	9.09

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ATOM	730	CA	SER	233	32.895	32.219	45.259	1.00	8.23
ATOM	731	CB	SER	233	34.207	31.869	44.581	1.00	7.47
ATOM	732	OG	SER	233	35.280	32.544	45.204	1.00	11.40
ATOM	733	C	SER	233	32.974	31.890	46.767	1.00	10.53
ATOM	734	O	SER	233	33.031	32.816	47.602	1.00	9.05
ATOM	735	N	PHE	234	33.020	30.600	47.111	1.00	8.96
ATOM	736	CA	PHE	234	33.081	30.177	48.516	1.00	8.36
ATOM	737	CB	PHE	234	33.069	28.647	48.630	1.00	8.82
ATOM	738	CG	PHE	234	31.719	28.043	48.389	1.00	7.88
ATOM	739	CD1	PHE	234	31.414	27.451	47.162	1.00	9.14
ATOM	740	CD2	PHE	234	30.733	28.098	49.381	1.00	7.40
ATOM	741	CE1	PHE	234	30.146	26.927	46.924	1.00	9.95
ATOM	742	CE2	PHE	234	29.461	27.585	49.162	1.00	9.69
ATOM	743	CZ	PHE	234	29.159	26.995	47.928	1.00	10.14
ATOM	744	C	PHE	234	34.303	30.744	49.227	1.00	10.56
ATOM	745	O	PHE	234	34.216	31.140	50.399	1.00	10.48
ATOM	746	N	ASP	235	35.434	30.804	48.529	1.00	10.70
ATOM	747	CA	ASP	235	36.644	31.338	49.139	1.00	11.77
ATOM	748	CB	ASP	235	37.909	30.652	48.584	1.00	10.84
ATOM	749	CG	ASP	235	38.130	30.903	47.097	1.00	16.86
ATOM	750	OD1	ASP	235	37.519	31.828	46.524	1.00	13.35
ATOM	751	OD2	ASP	235	38.933	30.152	46.491	1.00	21.65
ATOM	752	C	ASP	235	36.761	32.878	49.123	1.00	13.33
ATOM	753	O	ASP	235	37.852	33.423	49.350	1.00	15.58
ATOM	754	N	GLY	236	35.651	33.557	48.817	1.00	9.84
ATOM	755	CA	GLY	236	35.600	35.003	48.868	1.00	9.11
ATOM	756	C	GLY	236	36.040	35.864	47.715	1.00	11.25
ATOM	757	O	GLY	236	36.204	37.065	47.900	1.00	16.51
ATOM	758	N	ARG	237	36.178	35.308	46.527	1.00	10.63
ATOM	759	CA	ARG	237	36.584	36.099	45.372	1.00	10.06
ATOM	760	CB	ARG	237	37.541	35.290	44.495	1.00	13.52
ATOM	761	CG	ARG	237	38.918	35.068	45.112	1.00	13.17
ATOM	762	CD	ARG	237	39.705	34.088	44.269	1.00	12.67
ATOM	763	NE	ARG	237	39.162	32.749	44.416	1.00	14.67
ATOM	764	CZ	ARG	237	39.238	31.785	43.506	1.00	17.38
ATOM	765	NH1	ARG	237	39.846	31.995	42.352	1.00	17.60
ATOM	766	NH2	ARG	237	38.696	30.605	43.753	1.00	20.61
ATOM	767	C	ARG	237	35.404	36.570	44.524	1.00	11.45
ATOM	768	O	ARG	237	34.431	35.825	44.327	1.00	10.90
ATOM	769	N	ASP	238	35.469	37.820	44.063	1.00	10.87
ATOM	770	CA	ASP	238	34.418	38.365	43.205	1.00	11.26
ATOM	771	CB	ASP	238	34.500	39.894	43.168	1.00	12.93
ATOM	772	CG	ASP	238	33.423	40.532	42.284	1.00	15.24
ATOM	773	OD1	ASP	238	32.990	39.961	41.268	1.00	14.40
ATOM	774	OD2	ASP	238	33.027	41.658	42.585	1.00	19.77
ATOM	775	C	ASP	238	34.678	37.764	41.813	1.00	13.62
ATOM	776	O	ASP	238	35.700	38.052	41.163	1.00	12.96
ATOM	777	N	VAL	239	33.741	36.939	41.361	1.00	10.94
ATOM	778	CA	VAL	239	33.868	36.241	40.088	1.00	12.62
ATOM	779	CB	VAL	239	32.728	35.199	39.937	1.00	16.76
ATOM	780	CG1	VAL	239	31.396	35.879	39.691	1.00	14.71
ATOM	781	CG2	VAL	239	33.042	34.245	38.839	1.00	35.08
ATOM	782	C	VAL	239	33.967	37.137	38.841	1.00	14.13



ATOM	783	O	VAL	239	34.545	36.747	37.822	1.00	14.25
ATOM	784	N	LEU	240	33.418	38.342	38.919	1.00	15.56
ATOM	785	CA	LEU	240	33.481	39.256	37.783	1.00	18.76
ATOM	786	CB	LEU	240	32.330	40.270	37.819	1.00	20.08
ATOM	787	CG	LEU	240	31.783	40.672	36.446	1.00	28.99
ATOM	788	CD1	LEU	240	30.998	39.515	35.872	1.00	32.72
ATOM	789	CD2	LEU	240	30.894	41.884	36.569	1.00	34.23
ATOM	790	C	LEU	240	34.826	39.993	37.733	1.00	21.57
ATOM	791	O	LEU	240	35.367	40.230	36.652	1.00	23.34
ATOM	792	N	ARG	241	35.407	40.268	38.897	1.00	20.15
ATOM	793	CA	ARG	241	36.661	41.011	38.938	1.00	21.02
ATOM	794	CB	ARG	241	36.657	41.976	40.128	1.00	22.27
ATOM	795	CG	ARG	241	35.577	43.055	40.056	1.00	22.44
ATOM	796	CD	ARG	241	35.646	43.973	41.260	0.00	20.57
ATOM	797	NE	ARG	241	34.424	44.759	41.378	0.00	19.29
ATOM	798	CZ	ARG	241	34.218	45.931	40.780	0.00	18.55
ATOM	799	NH1	ARG	241	35.163	46.476	40.020	0.00	18.26
ATOM	800	NH2	ARG	241	33.040	46.532	40.896	0.00	18.26
ATOM	801	C	ARG	241	37.917	40.162	38.973	1.00	22.41
ATOM	802	O	ARG	241	39.017	40.673	38.793	1.00	24.72
ATOM	803	N	HIS	242	37.757	38.863	39.185	1.00	20.26
ATOM	804	CA	HIS	242	38.898	37.972	39.280	1.00	19.34
ATOM	805	CB	HIS	242	38.667	37.011	40.438	1.00	18.34
ATOM	806	CG	HIS	242	39.922	36.428	40.971	1.00	23.21
ATOM	807	CD2	HIS	242	40.667	36.764	42.052	1.00	24.92
ATOM	808	ND1	HIS	242	40.585	35.392	40.349	1.00	27.01
ATOM	809	CE1	HIS	242	41.690	35.114	41.019	1.00	28.51
ATOM	810	NE2	HIS	242	41.761	35.933	42.058	1.00	29.24
ATOM	811	C	HIS	242	39.216	37.205	37.989	1.00	17.20
ATOM	812	O	HIS	242	38.362	36.526	37.437	1.00	17.26
ATOM	813	N	PRO	243	40.484	37.199	37.563	1.00	17.89
ATOM	814	CD	PRO	243	41.647	37.855	38.194	1.00	20.85
ATOM	815	CA	PRO	243	40.875	36.500	36.330	1.00	16.49
ATOM	816	CB	PRO	243	42.316	36.970	36.112	1.00	20.92
ATOM	817	CG	PRO	243	42.822	37.158	37.525	1.00	19.91
ATOM	818	C	PRO	243	40.754	34.969	36.294	1.00	18.47
ATOM	819	O	PRO	243	40.859	34.371	35.216	1.00	19.70
ATOM	820	N	ALA	244	40.498	34.344	37.450	1.00	15.25
ATOM	821	CA	ALA	244	40.372	32.884	37.525	1.00	13.10
ATOM	822	CB	ALA	244	40.299	32.415	38.971	1.00	14.32
ATOM	823	C	ALA	244	39.166	32.384	36.735	1.00	12.10
ATOM	824	O	ALA	244	39.062	31.198	36.433	1.00	16.31
ATOM	825	N	TRP	245	38.236	33.288	36.448	1.00	11.10
ATOM	826	CA	TRP	245	37.057	32.974	35.633	1.00	12.47
ATOM	827	CB	TRP	245	35.765	33.331	36.371	1.00	11.95
ATOM	828	CG	TRP	245	35.490	32.473	37.579	1.00	11.69
ATOM	829	CD2	TRP	245	35.919	32.721	38.930	1.00	11.65
ATOM	830	CE2	TRP	245	35.415	31.669	39.726	1.00	11.33
ATOM	831	CE3	TRP	245	36.674	33.730	39.540	1.00	11.70
ATOM	832	CD1	TRP	245	34.763	31.317	37.614	1.00	12.75
ATOM	833	NE1	TRP	245	34.716	30.833	38.901	1.00	15.29
ATOM	834	CZ2	TRP	245	35.643	31.594	41.098	1.00	10.78
ATOM	835	CZ3	TRP	245	36.903	33.660	40.910	1.00	13.94

ATOM	836	CH2	TRP	245	36.386	32.594	41.673	1.00	14.46
ATOM	837	C	TRP	245	37.203	33.845	34.373	1.00	14.31
ATOM	838	O	TRP	245	36.743	34.989	34.336	1.00	16.32
ATOM	839	N	PRO	246	37.891	33.327	33.345	1.00	15.74
ATOM	840	CD	PRO	246	38.521	31.997	33.265	1.00	18.39
ATOM	841	CA	PRO	246	38.102	34.068	32.101	1.00	18.56
ATOM	842	CB	PRO	246	38.990	33.124	31.294	1.00	19.24
ATOM	843	CG	PRO	246	38.590	31.778	31.787	1.00	27.60
ATOM	844	C	PRO	246	36.830	34.439	31.349	1.00	18.21
ATOM	845	O	PRO	246	36.806	35.434	30.627	1.00	21.01
ATOM	846	N	GLN	247	35.779	33.638	31.496	1.00	15.33
ATOM	847	CA	GLN	247	34.520	33.930	30.825	1.00	15.65
ATOM	848	CB	GLN	247	34.173	32.812	29.854	1.00	21.68
ATOM	849	CG	GLN	247	35.265	32.635	28.812	1.00	29.04
ATOM	850	CD	GLN	247	34.750	32.067	27.533	1.00	41.63
ATOM	851	OE1	GLN	247	34.307	32.830	26.627	1.00	54.44
ATOM	852	NE2	GLN	247	34.818	30.747	27.395	1.00	38.76
ATOM	853	C	GLN	247	33.432	34.158	31.864	1.00	14.94
ATOM	854	O	GLN	247	33.169	33.310	32.719	1.00	15.97
ATOM	855	N	LYS	248	32.818	35.328	31.793	1.00	12.37
ATOM	856	CA	LYS	248	31.813	35.726	32.761	1.00	10.26
ATOM	857	CB	LYS	248	31.873	37.237	32.974	1.00	8.88
ATOM	858	CG	LYS	248	33.286	37.766	33.167	1.00	10.72
ATOM	859	CD	LYS	248	33.997	37.142	34.363	1.00	11.39
ATOM	860	CE	LYS	248	35.366	37.783	34.502	1.00	12.62
ATOM	861	NZ	LYS	248	36.167	37.202	35.606	1.00	13.55
ATOM	862	C	LYS	248	30.387	35.257	32.484	1.00	11.42
ATOM	863	O	LYS	248	29.427	36.023	32.651	1.00	14.70
ATOM	864	N	SER	249	30.261	33.997	32.067	1.00	9.53
ATOM	865	CA	SER	249	28.962	33.397	31.812	1.00	9.68
ATOM	866	CB	SER	249	28.889	32.805	30.401	1.00	12.41
ATOM	867	OG	SER	249	28.826	33.846	29.430	1.00	14.83
ATOM	868	C	SER	249	28.729	32.323	32.876	1.00	8.86
ATOM	869	O	SER	249	29.679	31.801	33.457	1.00	8.31
ATOM	870	N	VAL	250	27.464	32.021	33.120	1.00	9.03
ATOM	871	CA	VAL	250	27.055	31.044	34.123	1.00	10.67
ATOM	872	CB	VAL	250	26.186	31.731	35.210	1.00	13.24
ATOM	873	CG1	VAL	250	25.716	30.713	36.238	1.00	16.31
ATOM	874	CG2	VAL	250	26.969	32.847	35.887	1.00	17.56
ATOM	875	C	VAL	250	26.209	29.953	33.479	1.00	10.06
ATOM	876	O	VAL	250	25.302	30.252	32.688	1.00	8.85
ATOM	877	N	TRP	251	26.522	28.697	33.790	1.00	8.27
ATOM	878	CA	TRP	251	25.748	27.559	33.273	1.00	7.25
ATOM	879	CB	TRP	251	26.474	26.221	33.539	1.00	5.81
ATOM	880	CG	TRP	251	27.668	25.919	32.689	1.00	8.44
ATOM	881	CD2	TRP	251	27.697	25.804	31.253	1.00	7.01
ATOM	882	CE2	TRP	251	29.014	25.442	30.891	1.00	8.05
ATOM	883	CE3	TRP	251	26.735	25.982	30.243	1.00	11.41
ATOM	884	CD1	TRP	251	28.937	25.639	33.122	1.00	7.73
ATOM	885	NE1	TRP	251	29.750	25.349	32.044	1.00	9.29
ATOM	886	CZ2	TRP	251	29.401	25.250	29.548	1.00	10.00
ATOM	887	CZ3	TRP	251	27.131	25.794	28.883	1.00	11.74
ATOM	888	CH2	TRP	251	28.447	25.431	28.569	1.00	8.88



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ATOM	889	C	TRP	251	24.426	27.471	34.026	1.00	7.43
ATOM	890	O	TRP	251	24.381	27.713	35.231	1.00	8.02
ATOM	891	N	HIS	252	23.345	27.143	33.328	1.00	6.15
ATOM	892	CA	HIS	252	22.077	26.929	34.024	1.00	6.31
ATOM	893	CB	HIS	252	21.299	28.233	34.291	1.00	8.14
ATOM	894	CG	HIS	252	20.937	29.004	33.055	1.00	7.73
ATOM	895	CD2	HIS	252	21.407	30.176	32.565	1.00	9.83
ATOM	896	ND1	HIS	252	19.952	28.590	32.180	1.00	8.85
ATOM	897	CE1	HIS	252	19.834	29.477	31.199	1.00	8.72
ATOM	898	NE2	HIS	252	20.708	30.445	31.412	1.00	9.06
ATOM	899	C	HIS	252	21.179	25.836	33.413	1.00	7.71
ATOM	900	O	HIS	252	20.389	25.228	34.127	1.00	8.53
ATOM	901	N	GLY	253	21.281	25.611	32.099	1.00	8.03
ATOM	902	CA	GLY	253	20.474	24.592	31.430	1.00	7.38
ATOM	903	C	GLY	253	18.968	24.738	31.580	1.00	8.73
ATOM	904	O	GLY	253	18.253	23.743	31.447	1.00	10.24
ATOM	905	N	SER	254	18.475	25.974	31.735	1.00	7.94
ATOM	906	CA	SER	254	17.044	26.228	31.966	1.00	9.32
ATOM	907	CB	SER	254	16.823	26.635	33.428	1.00	8.58
ATOM	908	OG	SER	254	17.548	25.801	34.313	1.00	9.45
ATOM	909	C	SER	254	16.414	27.333	31.135	1.00	9.44
ATOM	910	O	SER	254	17.119	28.217	30.655	1.00	9.05
ATOM	911	N	ASP	255	15.085	27.294	31.018	1.00	9.69
ATOM	912	CA	ASP	255	14.370	28.355	30.328	1.00	10.56
ATOM	913	CB	ASP	255	13.078	27.873	29.644	1.00	11.81
ATOM	914	CG	ASP	255	11.970	27.480	30.603	1.00	16.63
ATOM	915	OD1	ASP	255	11.962	27.813	31.798	1.00	13.43
ATOM	916	OD2	ASP	255	11.042	26.822	30.125	1.00	20.81
ATOM	917	C	ASP	255	14.159	29.484	31.357	1.00	12.19
ATOM	918	O	ASP	255	14.563	29.347	32.517	1.00	8.72
ATOM	919	N	PRO	256	13.535	30.616	30.949	1.00	12.50
ATOM	920	CD	PRO	256	13.135	31.021	29.596	1.00	13.84
ATOM	921	CA	PRO	256	13.338	31.716	31.911	1.00	13.68
ATOM	922	CB	PRO	256	12.731	32.817	31.043	1.00	16.35
ATOM	923	CG	PRO	256	13.291	32.514	29.670	1.00	18.75
ATOM	924	C	PRO	256	12.501	31.437	33.141	1.00	14.48
ATOM	925	O	PRO	256	12.577	32.183	34.125	1.00	16.99
ATOM	926	N	SER	257	11.676	30.394	33.090	1.00	12.81
ATOM	927	CA	SER	257	10.855	30.046	34.243	1.00	13.26
ATOM	928	CB	SER	257	9.477	29.557	33.786	1.00	18.73
ATOM	929	OG	SER	257	9.580	28.367	33.026	1.00	28.07
ATOM	930	C	SER	257	11.537	28.987	35.128	1.00	11.91
ATOM	931	O	SER	257	10.952	28.501	36.092	1.00	13.55
ATOM	932	N	GLY	258	12.772	28.634	34.790	1.00	9.77
ATOM	933	CA	GLY	258	13.508	27.654	35.563	1.00	10.17
ATOM	934	C	GLY	258	13.238	26.204	35.211	1.00	12.95
ATOM	935	O	GLY	258	13.517	25.312	36.023	1.00	12.41
ATOM	936	N	ARG	259	12.664	25.952	34.039	1.00	11.66
ATOM	937	CA	ARG	259	12.387	24.580	33.636	1.00	12.36
ATOM	938	CB	ARG	259	11.078	24.502	32.860	1.00	15.24
ATOM	939	CG	ARG	259	9.829	24.886	33.661	1.00	19.16
ATOM	940	CD	ARG	259	8.609	24.876	32.766	0.00	16.18
ATOM	941	NE	ARG	259	8.818	25.731	31.601	0.00	14.78

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ATOM	942	CZ	ARG	259	7.995	26.702	31.219	0.00	13.66
ATOM	943	NH1	ARG	259	6.890	26.949	31.912	0.00	13.15
ATOM	944	NH2	ARG	259	8.311	27.470	30.185	0.00	13.15
ATOM	945	C	ARG	259	13.539	24.045	32.795	1.00	9.40
ATOM	946	O	ARG	259	14.193	24.797	32.072	1.00	11.64
ATOM	947	N	ARG	260	13.767	22.740	32.890	1.00	10.36
ATOM	948	CA	ARG	260	14.859	22.072	32.208	1.00	10.92
ATOM	949	CB	ARG	260	14.963	20.613	32.681	1.00	8.05
ATOM	950	CG	ARG	260	13.903	19.681	32.102	1.00	13.57
ATOM	951	CD	ARG	260	13.715	18.440	32.959	1.00	13.55
ATOM	952	NE	ARG	260	12.793	18.708	34.059	1.00	14.10
ATOM	953	CZ	ARG	260	12.264	17.784	34.852	1.00	15.72
ATOM	954	NH1	ARG	260	12.574	16.503	34.674	1.00	14.41
ATOM	955	NH2	ARG	260	11.392	18.141	35.792	1.00	16.24
ATOM	956	C	ARG	260	14.762	22.116	30.691	1.00	11.29
ATOM	957	O	ARG	260	13.659	22.063	30.137	1.00	13.57
ATOM	958	N	LEU	261	15.916	22.281	30.043	1.00	10.67
ATOM	959	CA	LEU	261	16.026	22.303	28.585	1.00	10.49
ATOM	960	CB	LEU	261	16.766	23.557	28.106	1.00	11.75
ATOM	961	CG	LEU	261	16.007	24.869	28.276	1.00	15.29
ATOM	962	CD1	LEU	261	16.865	26.025	27.794	1.00	14.39
ATOM	963	CD2	LEU	261	14.698	24.838	27.505	1.00	18.88
ATOM	964	C	LEU	261	16.802	21.044	28.207	1.00	11.08
ATOM	965	O	LEU	261	18.025	21.037	28.200	1.00	12.60
ATOM	966	N	MET	262	16.078	19.970	27.897	1.00	13.03
ATOM	967	CA	MET	262	16.694	18.697	27.572	1.00	15.60
ATOM	968	CB	MET	262	15.635	17.618	27.430	1.00	21.23
ATOM	969	CG	MET	262	14.861	17.413	28.728	1.00	42.59
ATOM	970	SD	MET	262	13.990	15.830	28.827	1.00	54.60
ATOM	971	CE	MET	262	14.754	15.114	30.316	1.00	55.07
ATOM	972	C	MET	262	17.610	18.714	26.379	1.00	15.15
ATOM	973	O	MET	262	18.499	17.880	26.283	1.00	18.38
ATOM	974	N	GLU	263	17.431	19.681	25.490	1.00	12.77
ATOM	975	CA	GLU	263	18.305	19.781	24.332	1.00	16.03
ATOM	976	CB	GLU	263	17.535	20.228	23.087	1.00	20.28
ATOM	977	CG	GLU	263	16.352	19.339	22.712	1.00	34.89
ATOM	978	CD	GLU	263	16.755	17.925	22.342	1.00	42.80
ATOM	979	OE1	GLU	263	17.894	17.723	21.865	1.00	45.67
ATOM	980	OE2	GLU	263	15.918	17.014	22.527	1.00	55.63
ATOM	981	C	GLU	263	19.433	20.770	24.597	1.00	17.27
ATOM	982	O	GLU	263	20.280	20.998	23.730	1.00	16.53
ATOM	983	N	SER	264	19.464	21.355	25.791	1.00	13.09
ATOM	984	CA	SER	264	20.502	22.324	26.082	1.00	10.58
ATOM	985	CB	SER	264	20.071	23.722	25.646	1.00	9.25
ATOM	986	OG	SER	264	21.226	24.498	25.380	1.00	16.12
ATOM	987	C	SER	264	20.995	22.332	27.528	1.00	10.61
ATOM	988	O	SER	264	20.949	23.349	28.233	1.00	10.80
ATOM	989	N	TYR	265	21.450	21.170	27.966	1.00	8.72
ATOM	990	CA	TYR	265	22.023	21.048	29.289	1.00	10.84
ATOM	991	CB	TYR	265	20.977	20.760	30.380	1.00	11.87
ATOM	992	CG	TYR	265	20.152	19.491	30.297	1.00	8.78
ATOM	993	CD1	TYR	265	19.093	19.305	31.188	1.00	8.95
ATOM	994	CE1	TYR	265	18.308	18.157	31.162	1.00	11.41

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ATOM	995	CD2	TYR	265	20.419	18.484	29.360	1.00	11.39
ATOM	996	CE2	TYR	265	19.634	17.313	29.326	1.00	12.07
ATOM	997	CZ	TYR	265	18.585	17.164	30.234	1.00	17.30
ATOM	998	OH	TYR	265	17.826	16.018	30.249	1.00	16.79
ATOM	999	C	TYR	265	23.211	20.088	29.311	1.00	9.39
ATOM	1000	O	TYR	265	23.467	19.382	30.293	1.00	8.37
ATOM	1001	N	CYS	266	23.974	20.129	28.214	1.00	8.27
ATOM	1002	CA	CYS	266	25.182	19.321	28.046	1.00	8.39
ATOM	1003	C	CYS	266	24.988	17.852	28.419	1.00	7.82
ATOM	1004	O	CYS	266	25.821	17.271	29.107	1.00	8.83
ATOM	1005	CB	CYS	266	26.337	19.943	28.829	1.00	9.42
ATOM	1006	SG	CYS	266	26.763	21.610	28.237	1.00	8.90
ATOM	1007	N	GLU	267	23.880	17.276	27.953	1.00	8.61
ATOM	1008	CA	GLU	267	23.544	15.882	28.221	1.00	11.70
ATOM	1009	CB	GLU	267	24.482	14.981	27.419	1.00	12.76
ATOM	1010	CG	GLU	267	24.305	15.265	25.908	1.00	24.58
ATOM	1011	CD	GLU	267	25.377	14.673	25.007	1.00	39.48
ATOM	1012	OE1	GLU	267	26.129	13.772	25.444	1.00	42.95
ATOM	1013	OE2	GLU	267	25.449	15.126	23.841	1.00	49.08
ATOM	1014	C	GLU	267	23.589	15.643	29.736	1.00	11.52
ATOM	1015	O	GLU	267	24.287	14.758	30.254	1.00	11.15
ATOM	1016	N	THR	268	22.792	16.465	30.410	1.00	9.46
ATOM	1017	CA	THR	268	22.679	16.498	31.857	1.00	9.65
ATOM	1018	CB	THR	268	21.712	15.407	32.440	1.00	15.01
ATOM	1019	OG1	THR	268	21.413	15.713	33.815	1.00	18.73
ATOM	1020	CG2	THR	268	22.279	14.019	32.324	1.00	12.06
ATOM	1021	C	THR	268	24.050	16.618	32.532	1.00	10.00
ATOM	1022	O	THR	268	24.381	15.918	33.488	1.00	10.46
ATOM	1023	N	TRP	269	24.840	17.557	32.002	1.00	8.83
ATOM	1024	CA	TRP	269	26.164	17.914	32.514	1.00	7.33
ATOM	1025	CB	TRP	269	26.014	18.593	33.886	1.00	6.91
ATOM	1026	CG	TRP	269	24.941	19.645	33.833	1.00	7.44
ATOM	1027	CD2	TRP	269	24.977	20.858	33.063	1.00	9.25
ATOM	1028	CE2	TRP	269	23.702	21.468	33.182	1.00	9.60
ATOM	1029	CE3	TRP	269	25.963	21.482	32.280	1.00	9.02
ATOM	1030	CD1	TRP	269	23.688	19.578	34.380	1.00	8.91
ATOM	1031	NE1	TRP	269	22.936	20.667	33.990	1.00	9.46
ATOM	1032	CZ2	TRP	269	23.391	22.678	32.542	1.00	10.78
ATOM	1033	CZ3	TRP	269	25.655	22.676	31.648	1.00	8.88
ATOM	1034	CH2	TRP	269	24.384	23.260	31.780	1.00	9.58
ATOM	1035	C	TRP	269	27.167	16.784	32.539	1.00	9.24
ATOM	1036	O	TRP	269	27.993	16.668	33.447	1.00	9.17
ATOM	1037	N	ARG	270	27.130	15.987	31.482	1.00	8.34
ATOM	1038	CA	ARG	270	28.034	14.867	31.364	1.00	10.31
ATOM	1039	CB	ARG	270	27.237	13.561	31.218	1.00	12.83
ATOM	1040	CG	ARG	270	26.506	13.153	32.487	1.00	13.79
ATOM	1041	CD	ARG	270	25.929	11.744	32.374	1.00	21.22
ATOM	1042	NE	ARG	270	25.323	11.363	33.649	1.00	39.86
ATOM	1043	CZ	ARG	270	24.063	10.953	33.798	1.00	53.84
ATOM	1044	NH1	ARG	270	23.261	10.841	32.736	1.00	52.16
ATOM	1045	NH2	ARG	270	23.568	10.778	35.023	1.00	58.09
ATOM	1046	C	ARG	270	29.045	14.999	30.223	1.00	13.63
ATOM	1047	O	ARG	270	30.025	14.251	30.173	1.00	17.45

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ATOM	1048	N	THR	271	28.874	15.987	29.356	1.00	10.29
ATOM	1049	CA	THR	271	29.799	16.117	28.250	1.00	10.70
ATOM	1050	CB	THR	271	29.112	15.726	26.918	1.00	12.98
ATOM	1051	OG1	THR	271	30.104	15.625	25.875	1.00	14.76
ATOM	1052	CG2	THR	271	28.065	16.768	26.533	1.00	11.47
ATOM	1053	C	THR	271	30.374	17.510	28.087	1.00	7.92
ATOM	1054	O	THR	271	29.717	18.501	28.412	1.00	12.00
ATOM	1055	N	GLU	272	31.614	17.571	27.620	1.00	8.88
ATOM	1056	CA	GLU	272	32.267	18.841	27.346	1.00	11.22
ATOM	1057	CB	GLU	272	33.478	19.069	28.262	1.00	12.02
ATOM	1058	CG	GLU	272	34.634	18.058	28.148	1.00	13.79
ATOM	1059	CD	GLU	272	35.909	18.622	28.765	1.00	24.86
ATOM	1060	OE1	GLU	272	36.848	18.971	28.013	1.00	26.85
ATOM	1061	OE2	GLU	272	35.958	18.761	30.005	1.00	25.32
ATOM	1062	C	GLU	272	32.658	18.909	25.852	1.00	12.64
ATOM	1063	O	GLU	272	33.504	19.716	25.453	1.00	14.03
ATOM	1064	N	THR	273	32.010	18.087	25.029	1.00	11.26
ATOM	1065	CA	THR	273	32.280	18.071	23.588	1.00	12.66
ATOM	1066	CB	THR	273	31.516	16.922	22.895	1.00	16.48
ATOM	1067	OG1	THR	273	31.987	16.778	21.551	1.00	32.58
ATOM	1068	CG2	THR	273	30.030	17.194	22.871	1.00	15.77
ATOM	1069	C	THR	273	31.886	19.423	22.972	1.00	13.21
ATOM	1070	O	THR	273	30.926	20.065	23.441	1.00	13.27
ATOM	1071	N	THR	274	32.600	19.860	21.925	1.00	10.07
ATOM	1072	CA	THR	274	32.291	21.165	21.326	1.00	10.48
ATOM	1073	CB	THR	274	33.375	21.663	20.341	1.00	11.25
ATOM	1074	OG1	THR	274	33.429	20.802	19.198	1.00	11.26
ATOM	1075	CG2	THR	274	34.731	21.714	21.005	1.00	12.70
ATOM	1076	C	THR	274	30.948	21.290	20.631	1.00	11.19
ATOM	1077	O	THR	274	30.374	22.380	20.588	1.00	13.84
ATOM	1078	N	GLY	275	30.461	20.183	20.081	1.00	12.95
ATOM	1079	CA	GLY	275	29.195	20.186	19.381	1.00	13.46
ATOM	1080	C	GLY	275	27.961	20.216	20.255	1.00	16.29
ATOM	1081	O	GLY	275	26.895	20.612	19.788	1.00	22.92
ATOM	1082	N	ALA	276	28.066	19.791	21.507	1.00	12.83
ATOM	1083	CA	ALA	276	26.894	19.806	22.381	1.00	12.40
ATOM	1084	CB	ALA	276	27.033	18.746	23.452	1.00	10.70
ATOM	1085	C	ALA	276	26.742	21.191	23.021	1.00	10.43
ATOM	1086	O	ALA	276	27.735	21.912	23.164	1.00	10.44
ATOM	1087	N	THR	277	25.516	21.558	23.399	1.00	9.22
ATOM	1088	CA	THR	277	25.301	22.855	24.029	1.00	9.06
ATOM	1089	CB	THR	277	24.491	23.849	23.140	1.00	14.14
ATOM	1090	OG1	THR	277	23.154	23.370	22.969	1.00	21.05
ATOM	1091	CG2	THR	277	25.167	24.048	21.787	1.00	17.07
ATOM	1092	C	THR	277	24.606	22.800	25.379	1.00	10.02
ATOM	1093	O	THR	277	23.905	21.830	25.720	1.00	10.24
ATOM	1094	N	GLY	278	24.784	23.888	26.120	1.00	10.62
ATOM	1095	CA	GLY	278	24.158	24.054	27.413	1.00	10.07
ATOM	1096	C	GLY	278	23.663	25.485	27.473	1.00	9.01
ATOM	1097	O	GLY	278	24.303	26.386	26.923	1.00	10.30
ATOM	1098	N	GLN	279	22.519	25.701	28.106	1.00	7.20
ATOM	1099	CA	GLN	279	21.982	27.050	28.216	1.00	7.37
ATOM	1100	CB	GLN	279	20.487	27.024	28.524	1.00	6.93

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ATOM	1101	CG	GLN	279	19.724	28.188	27.921	1.00	7.69
ATOM	1102	CD	GLN	279	19.459	28.006	26.419	1.00	14.20
ATOM	1103	OE1	GLN	279	20.091	27.189	25.745	1.00	12.46
ATOM	1104	NE2	GLN	279	18.504	28.751	25.906	1.00	13.42
ATOM	1105	C	GLN	279	22.773	27.799	29.302	1.00	8.48
ATOM	1106	O	GLN	279	22.940	27.313	30.423	1.00	8.67
ATOM	1107	N	ALA	280	23.261	28.977	28.949	1.00	7.19
ATOM	1108	CA	ALA	280	24.089	29.772	29.838	1.00	7.73
ATOM	1109	CB	ALA	280	25.561	29.646	29.434	1.00	9.40
ATOM	1110	C	ALA	280	23.663	31.223	29.790	1.00	9.97
ATOM	1111	O	ALA	280	22.879	31.618	28.924	1.00	11.40
ATOM	1112	N	SER	281	24.165	32.007	30.740	1.00	9.84
ATOM	1113	CA	SER	281	23.823	33.413	30.831	1.00	9.93
ATOM	1114	CB	SER	281	22.830	33.602	31.969	1.00	8.72
ATOM	1115	OG	SER	281	22.456	34.970	32.080	1.00	10.75
ATOM	1116	C	SER	281	25.050	34.280	31.096	1.00	13.00
ATOM	1117	O	SER	281	25.897	33.935	31.918	1.00	11.02
ATOM	1118	N	SER	282	25.108	35.438	30.442	1.00	10.37
ATOM	1119	CA	SER	282	26.212	36.346	30.646	1.00	9.96
ATOM	1120	CB	SER	282	26.384	37.281	29.455	1.00	11.10
ATOM	1121	OG	SER	282	27.539	38.081	29.646	1.00	15.65
ATOM	1122	C	SER	282	25.952	37.197	31.865	1.00	10.90
ATOM	1123	O	SER	282	24.996	37.957	31.910	1.00	12.82
ATOM	1124	N	LEU	283	26.849	37.111	32.829	1.00	11.53
ATOM	1125	CA	LEU	283	26.740	37.901	34.035	1.00	14.28
ATOM	1126	CB	LEU	283	27.725	37.361	35.070	1.00	19.36
ATOM	1127	CG	LEU	283	27.228	37.238	36.502	1.00	28.95
ATOM	1128	CD1	LEU	283	25.814	36.665	36.542	1.00	25.11
ATOM	1129	CD2	LEU	283	28.213	36.355	37.248	1.00	33.05
ATOM	1130	C	LEU	283	27.030	39.382	33.724	1.00	16.05
ATOM	1131	O	LEU	283	26.673	40.272	34.507	1.00	16.78
ATOM	1132	N	LEU	284	27.673	39.646	32.586	1.00	14.06
ATOM	1133	CA	LEU	284	27.974	41.018	32.191	1.00	16.31
ATOM	1134	CB	LEU	284	28.930	41.058	30.989	1.00	13.83
ATOM	1135	CG	LEU	284	30.296	40.405	31.242	1.00	14.35
ATOM	1136	CD1	LEU	284	31.078	40.305	29.965	1.00	16.51
ATOM	1137	CD2	LEU	284	31.062	41.159	32.276	1.00	16.99
ATOM	1138	C	LEU	284	26.683	41.778	31.886	1.00	18.57
ATOM	1139	O	LEU	284	26.626	42.995	32.054	1.00	22.25
ATOM	1140	N	SER	285	25.635	41.062	31.490	1.00	16.42
ATOM	1141	CA	SER	285	24.348	41.692	31.194	1.00	18.85
ATOM	1142	CB	SER	285	23.585	40.869	30.154	1.00	17.75
ATOM	1143	OG	SER	285	23.058	39.678	30.723	1.00	22.16
ATOM	1144	C	SER	285	23.480	41.867	32.454	1.00	19.12
ATOM	1145	O	SER	285	22.353	42.347	32.367	1.00	22.78
ATOM	1146	N	GLY	286	24.002	41.463	33.611	1.00	18.11
ATOM	1147	CA	GLY	286	23.262	41.568	34.857	1.00	17.95
ATOM	1148	C	GLY	286	22.170	40.528	35.071	1.00	19.04
ATOM	1149	O	GLY	286	21.418	40.638	36.034	1.00	20.27
ATOM	1150	N	ARG	287	22.129	39.475	34.251	1.00	15.86
ATOM	1151	CA	ARG	287	21.088	38.447	34.374	1.00	12.80
ATOM	1152	CB	ARG	287	20.240	38.400	33.097	1.00	12.46
ATOM	1153	CG	ARG	287	19.505	39.678	32.804	1.00	14.92



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ATOM	1154	CD	ARG	287	18.968	39.685	31.378	1.00	25.50
ATOM	1155	NE	ARG	287	20.036	39.683	30.378	1.00	25.57
ATOM	1156	CZ	ARG	287	19.847	39.560	29.066	1.00	27.33
ATOM	1157	NH1	ARG	287	18.625	39.430	28.571	1.00	25.30
ATOM	1158	NH2	ARG	287	20.889	39.558	28.246	1.00	25.11
ATOM	1159	C	ARG	287	21.663	37.056	34.613	1.00	12.17
ATOM	1160	O	ARG	287	22.758	36.743	34.142	1.00	13.69
ATOM	1161	N	LEU	288	20.893	36.213	35.300	1.00	10.50
ATOM	1162	CA	LEU	288	21.293	34.830	35.585	1.00	12.07
ATOM	1163	CB	LEU	288	20.855	34.420	36.993	1.00	11.10
ATOM	1164	CG	LEU	288	21.497	35.098	38.187	1.00	13.11
ATOM	1165	CD1	LEU	288	20.843	34.559	39.460	1.00	14.89
ATOM	1166	CD2	LEU	288	22.974	34.818	38.182	1.00	16.30
ATOM	1167	C	LEU	288	20.669	33.821	34.633	1.00	11.63
ATOM	1168	O	LEU	288	21.181	32.719	34.493	1.00	11.03
ATOM	1169	N	LEU	289	19.574	34.201	33.975	1.00	10.91
ATOM	1170	CA	LEU	289	18.843	33.273	33.113	1.00	11.22
ATOM	1171	CB	LEU	289	17.479	32.923	33.751	1.00	12.01
ATOM	1172	CG	LEU	289	17.476	32.243	35.134	1.00	12.63
ATOM	1173	CD1	LEU	289	16.068	32.236	35.706	1.00	12.30
ATOM	1174	CD2	LEU	289	18.024	30.808	35.019	1.00	12.35
ATOM	1175	C	LEU	289	18.663	33.681	31.648	1.00	11.78
ATOM	1176	O	LEU	289	17.668	33.342	31.018	1.00	12.35
ATOM	1177	N	GLU	290	19.634	34.409	31.116	1.00	11.86
ATOM	1178	CA	GLU	290	19.635	34.789	29.714	1.00	13.35
ATOM	1179	CB	GLU	290	20.924	35.555	29.430	1.00	17.02
ATOM	1180	CG	GLU	290	21.092	36.101	28.037	1.00	40.20
ATOM	1181	CD	GLU	290	22.326	36.986	27.919	1.00	49.50
ATOM	1182	OE1	GLU	290	23.203	36.932	28.803	1.00	39.91
ATOM	1183	OE2	GLU	290	22.438	37.741	26.930	1.00	62.69
ATOM	1184	C	GLU	290	19.593	33.460	28.944	1.00	14.01
ATOM	1185	O	GLU	290	20.058	32.421	29.435	1.00	14.47
ATOM	1186	N	GLN	291	19.030	33.475	27.752	1.00	13.28
ATOM	1187	CA	GLN	291	18.896	32.249	26.974	1.00	13.39
ATOM	1188	CB	GLN	291	17.476	32.180	26.437	1.00	12.23
ATOM	1189	CG	GLN	291	16.468	32.161	27.568	1.00	13.53
ATOM	1190	CD	GLN	291	16.552	30.881	28.348	1.00	12.24
ATOM	1191	OE1	GLN	291	16.370	29.816	27.786	1.00	13.87
ATOM	1192	NE2	GLN	291	16.867	30.971	29.631	1.00	10.73
ATOM	1193	C	GLN	291	19.910	32.045	25.858	1.00	15.73
ATOM	1194	O	GLN	291	19.572	32.170	24.676	1.00	21.34
ATOM	1195	N	LYS	292	21.154	31.763	26.237	1.00	13.25
ATOM	1196	CA	LYS	292	22.221	31.524	25.283	1.00	13.64
ATOM	1197	CB	LYS	292	23.471	32.325	25.656	1.00	15.76
ATOM	1198	CG	LYS	292	23.494	33.772	25.221	0.00	14.29
ATOM	1199	CD	LYS	292	24.929	34.283	25.262	0.00	13.82
ATOM	1200	CE	LYS	292	25.038	35.744	24.875	0.00	13.29
ATOM	1201	NZ	LYS	292	24.457	36.626	25.903	0.00	12.93
ATOM	1202	C	LYS	292	22.600	30.048	25.236	1.00	16.34
ATOM	1203	O	LYS	292	22.889	29.446	26.266	1.00	16.97
ATOM	1204	N	ALA	293	22.594	29.460	24.041	1.00	15.29
ATOM	1205	CA	ALA	293	22.998	28.066	23.877	1.00	15.09
ATOM	1206	CB	ALA	293	22.305	27.458	22.691	1.00	17.19

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ATOM	1207	C	ALA	293	24.501	28.141	23.627	1.00	18.98
ATOM	1208	O	ALA	293	24.930	28.682	22.594	1.00	22.49
ATOM	1209	N	ALA	294	25.298	27.698	24.602	1.00	15.43
ATOM	1210	CA	ALA	294	26.763	27.748	24.498	1.00	13.78
ATOM	1211	CB	ALA	294	27.353	28.469	25.729	1.00	10.17
ATOM	1212	C	ALA	294	27.390	26.362	24.370	1.00	12.39
ATOM	1213	O	ALA	294	26.869	25.389	24.914	1.00	11.83
ATOM	1214	N	SER	295	28.494	26.266	23.636	1.00	9.52
ATOM	1215	CA	SER	295	29.185	24.989	23.493	1.00	10.89
ATOM	1216	CB	SER	295	30.450	25.148	22.646	1.00	10.02
ATOM	1217	OG	SER	295	31.295	24.013	22.720	1.00	10.54
ATOM	1218	C	SER	295	29.594	24.502	24.884	1.00	9.64
ATOM	1219	O	SER	295	30.166	25.262	25.683	1.00	9.24
ATOM	1220	N	CYS	296	29.386	23.212	25.112	1.00	8.90
ATOM	1221	CA	CYS	296	29.709	22.581	26.380	1.00	10.24
ATOM	1222	C	CYS	296	31.188	22.555	26.696	1.00	9.59
ATOM	1223	O	CYS	296	31.588	22.266	27.829	1.00	9.50
ATOM	1224	CB	CYS	296	29.128	21.175	26.412	1.00	8.51
ATOM	1225	SG	CYS	296	27.315	21.214	26.322	1.00	10.52
ATOM	1226	N	HIS	297	32.012	22.842	25.698	1.00	8.62
ATOM	1227	CA	HIS	297	33.440	22.851	25.908	1.00	9.50
ATOM	1228	CB	HIS	297	34.166	22.677	24.576	1.00	9.64
ATOM	1229	CG	HIS	297	35.613	22.358	24.735	1.00	9.70
ATOM	1230	CD2	HIS	297	36.233	21.199	25.039	1.00	15.57
ATOM	1231	ND1	HIS	297	36.598	23.310	24.621	1.00	14.69
ATOM	1232	CE1	HIS	297	37.774	22.750	24.848	1.00	19.73
ATOM	1233	NE2	HIS	297	37.578	21.468	25.103	1.00	23.00
ATOM	1234	C	HIS	297	33.935	24.116	26.667	1.00	9.12
ATOM	1235	O	HIS	297	35.090	24.185	27.104	1.00	11.63
ATOM	1236	N	ASN	298	33.069	25.119	26.789	1.00	8.35
ATOM	1237	CA	ASN	298	33.405	26.337	27.522	1.00	8.97
ATOM	1238	CB	ASN	298	32.316	27.395	27.299	1.00	8.79
ATOM	1239	CG	ASN	298	32.437	28.090	25.952	1.00	8.51
ATOM	1240	OD1	ASN	298	33.344	28.879	25.735	1.00	11.82
ATOM	1241	ND2	ASN	298	31.508	27.812	25.062	1.00	11.49
ATOM	1242	C	ASN	298	33.490	26.063	29.037	1.00	10.39
ATOM	1243	O	ASN	298	32.731	25.244	29.571	1.00	11.28
ATOM	1244	N	SER	299	34.384	26.782	29.711	1.00	10.29
ATOM	1245	CA	SER	299	34.559	26.686	31.166	1.00	10.47
ATOM	1246	CB	SER	299	36.045	26.616	31.559	1.00	14.97
ATOM	1247	OG	SER	299	36.576	25.322	31.310	1.00	28.18
ATOM	1248	C	SER	299	33.915	27.945	31.732	1.00	10.29
ATOM	1249	O	SER	299	34.470	29.039	31.604	1.00	11.16
ATOM	1250	N	TYR	300	32.726	27.772	32.313	1.00	9.29
ATOM	1251	CA	TYR	300	31.918	28.856	32.859	1.00	8.49
ATOM	1252	CB	TYR	300	30.518	28.814	32.206	1.00	7.10
ATOM	1253	CG	TYR	300	30.426	29.295	30.764	1.00	7.59
ATOM	1254	CD1	TYR	300	31.445	30.062	30.183	1.00	10.11
ATOM	1255	CE1	TYR	300	31.326	30.561	28.876	1.00	9.19
ATOM	1256	CD2	TYR	300	29.296	29.016	30.004	1.00	8.62
ATOM	1257	CE2	TYR	300	29.166	29.499	28.714	1.00	11.31
ATOM	1258	CZ	TYR	300	30.184	30.269	28.156	1.00	12.94
ATOM	1259	OH	TYR	300	30.041	30.731	26.871	1.00	16.38



ATOM	1260	C	TYR	300	31.742	28.745	34.385	1.00	9.73
ATOM	1261	O	TYR	300	32.102	27.744	35.013	1.00	8.08
ATOM	1262	N	ILE	301	31.188	29.808	34.947	1.00	7.28
ATOM	1263	CA	ILE	301	30.888	29.902	36.358	1.00	7.35
ATOM	1264	CB	ILE	301	30.413	31.337	36.707	1.00	7.56
ATOM	1265	CG2	ILE	301	29.979	31.432	38.185	1.00	9.38
ATOM	1266	CG1	ILE	301	31.522	32.345	36.383	1.00	10.75
ATOM	1267	CD1	ILE	301	31.026	33.774	36.266	1.00	11.79
ATOM	1268	C	ILE	301	29.724	28.955	36.671	1.00	7.08
ATOM	1269	O	ILE	301	28.794	28.801	35.873	1.00	7.60
ATOM	1270	N	VAL	302	29.804	28.300	37.821	1.00	6.56
ATOM	1271	CA	VAL	302	28.729	27.441	38.274	1.00	6.59
ATOM	1272	CB	VAL	302	29.159	25.960	38.347	1.00	7.08
ATOM	1273	CG1	VAL	302	28.029	25.130	38.948	1.00	9.28
ATOM	1274	CG2	VAL	302	29.511	25.448	36.931	1.00	8.65
ATOM	1275	C	VAL	302	28.363	27.949	39.659	1.00	7.34
ATOM	1276	O	VAL	302	29.260	28.166	40.504	1.00	9.31
ATOM	1277	N	LEU	303	27.065	28.165	39.878	1.00	5.98
ATOM	1278	CA	LEU	303	26.566	28.643	41.168	1.00	6.62
ATOM	1279	CB	LEU	303	25.520	29.748	40.951	1.00	5.91
ATOM	1280	CG	LEU	303	25.974	30.946	40.105	1.00	5.79
ATOM	1281	CD1	LEU	303	24.809	31.914	39.936	1.00	9.29
ATOM	1282	CD2	LEU	303	27.168	31.626	40.751	1.00	8.55
ATOM	1283	C	LEU	303	25.934	27.525	42.012	1.00	6.94
ATOM	1284	O	LEU	303	25.483	26.493	41.483	1.00	7.50
ATOM	1285	N	CYS	304	25.895	27.758	43.323	1.00	5.58
ATOM	1286	CA	CYS	304	25.292	26.843	44.290	1.00	6.15
ATOM	1287	C	CYS	304	24.297	27.684	45.079	1.00	7.15
ATOM	1288	O	CYS	304	24.600	28.826	45.461	1.00	8.17
ATOM	1289	CB	CYS	304	26.329	26.294	45.275	1.00	7.42
ATOM	1290	SG	CYS	304	27.741	25.452	44.518	1.00	7.96
ATOM	1291	N	ILE	305	23.114	27.132	45.286	1.00	6.12
ATOM	1292	CA	ILE	305	22.064	27.815	46.020	1.00	7.49
ATOM	1293	CB	ILE	305	20.779	28.031	45.115	1.00	7.52
ATOM	1294	CG2	ILE	305	20.332	26.704	44.452	1.00	9.27
ATOM	1295	CG1	ILE	305	19.628	28.676	45.913	1.00	10.13
ATOM	1296	CD1	ILE	305	19.824	30.143	46.247	1.00	11.16
ATOM	1297	C	ILE	305	21.698	27.046	47.293	1.00	10.06
ATOM	1298	O	ILE	305	21.602	25.813	47.287	1.00	9.16
ATOM	1299	N	GLU	306	21.565	27.784	48.393	1.00	7.92
ATOM	1300	CA	GLU	306	21.152	27.232	49.690	1.00	10.18
ATOM	1301	CB	GLU	306	21.306	28.317	50.739	1.00	10.07
ATOM	1302	CG	GLU	306	21.335	27.819	52.146	1.00	13.04
ATOM	1303	CD	GLU	306	21.750	28.908	53.124	1.00	20.14
ATOM	1304	OE1	GLU	306	21.900	30.077	52.706	1.00	10.57
ATOM	1305	OE2	GLU	306	21.934	28.603	54.320	1.00	24.88
ATOM	1306	C	GLU	306	19.881	26.872	49.478	1.00	9.73
ATOM	1307	O	GLU	306	18.873	27.739	49.139	1.00	11.98
ATOM	1308	N	ASN	307	19.322	25.606	49.677	1.00	10.68
ATOM	1309	CA	ASN	307	17.960	25.186	49.355	1.00	13.13
ATOM	1310	CB	ASN	307	17.937	23.747	48.816	1.00	17.30
ATOM	1311	CG	ASN	307	18.054	22.697	49.904	1.00	33.21
ATOM	1312	OD1	ASN	307	17.751	21.521	49.665	1.00	42.13

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ATOM	1313	ND2 ASN	307	18.483	23.099	51.104	1.00	34.89
ATOM	1314	C ASN	307	16.836	25.438	50.343	1.00	13.53
ATOM	1315	O ASN	307	15.665	25.234	50.028	1.00	14.73
ATOM	1316	N SER	308	17.199	25.938	51.513	1.00	15.33
ATOM	1317	CA SER	308	16.228	26.268	52.540	1.00	17.72
ATOM	1318	CB SER	308	15.658	24.992	53.155	1.00	21.56
ATOM	1319	OG SER	308	16.711	24.160	53.619	1.00	25.37
ATOM	1320	C SER	308	16.937	27.062	53.621	1.00	16.82
ATOM	1321	O SER	308	18.156	26.967	53.754	1.00	17.25
ATOM	1322	N PHE	309	16.193	27.911	54.318	1.00	19.67
ATOM	1323	CA PHE	309	16.754	28.674	55.429	1.00	21.81
ATOM	1324	CB PHE	309	16.009	30.000	55.650	1.00	19.28
ATOM	1325	CG PHE	309	16.483	30.765	56.855	0.00	20.57
ATOM	1326	CD1 PHE	309	17.742	31.357	56.868	0.00	20.77
ATOM	1327	CD2 PHE	309	15.676	30.887	57.983	0.00	20.76
ATOM	1328	CE1 PHE	309	18.193	32.058	57.987	0.00	21.12
ATOM	1329	CE2 PHE	309	16.116	31.586	59.108	0.00	21.12
ATOM	1330	CZ PHE	309	17.379	32.173	59.109	0.00	21.23
ATOM	1331	C PHE	309	16.563	27.762	56.635	1.00	22.35
ATOM	1332	O PHE	309	17.541	27.533	57.353	1.00	26.83
ATOM	1333	OT PHE	309	15.440	27.254	56.828	1.00	26.72
ATOM	1334	OW WAT	401	35.042	31.373	33.454	1.00	14.12
ATOM	1335	OW WAT	402	28.187	34.855	46.584	1.00	7.88
ATOM	1336	OW WAT	403	35.662	26.376	49.640	1.00	11.26
ATOM	1337	OW WAT	404	25.161	27.442	37.820	1.00	10.17
ATOM	1338	OW WAT	405	32.569	28.701	39.266	1.00	8.09
ATOM	1339	OW WAT	406	23.115	17.509	48.067	1.00	15.06
ATOM	1340	OW WAT	407	23.144	14.278	35.669	1.00	17.19
ATOM	1341	OW WAT	408	12.544	33.294	48.204	1.00	12.28
ATOM	1342	OW WAT	409	24.735	12.279	37.713	1.00	21.94
ATOM	1343	OW WAT	410	31.247	14.687	32.770	1.00	19.39
ATOM	1344	OW WAT	411	21.080	20.697	41.768	1.00	13.46
ATOM	1345	OW WAT	412	21.911	18.669	26.262	1.00	16.11
ATOM	1346	OW WAT	413	12.899	34.774	34.572	1.00	13.93
ATOM	1347	OW WAT	414	15.656	21.976	25.008	1.00	20.91
ATOM	1348	OW WAT	415	29.212	28.531	22.036	1.00	16.40
ATOM	1349	OW WAT	416	24.593	28.373	55.308	1.00	34.65
ATOM	1350	OW WAT	417	35.097	24.019	41.496	1.00	22.94
ATOM	1351	OW WAT	418	18.566	14.927	37.495	1.00	18.73
ATOM	1352	OW WAT	419	35.149	17.242	31.998	1.00	23.10
ATOM	1353	OW WAT	420	20.849	31.117	55.292	1.00	21.98
ATOM	1354	OW WAT	421	30.294	39.756	40.658	1.00	20.87
ATOM	1355	OW WAT	422	11.858	19.238	39.364	1.00	30.37
ATOM	1356	OW WAT	423	13.182	20.311	28.140	1.00	20.79
ATOM	1357	OW WAT	424	20.499	46.290	51.202	1.00	15.88
ATOM	1358	OW WAT	425	14.486	29.276	25.815	1.00	30.27
ATOM	1359	OW WAT	426	20.437	9.743	35.300	1.00	57.70
ATOM	1360	OW WAT	427	8.107	23.588	51.829	1.00	30.09
ATOM	1361	OW WAT	428	26.082	42.690	45.786	1.00	21.81
ATOM	1362	OW WAT	429	31.932	22.876	57.878	1.00	32.40
ATOM	1363	OW WAT	430	28.484	39.973	38.870	1.00	58.83
ATOM	1364	OW WAT	431	19.349	19.830	39.454	1.00	21.54
ATOM	1365	OW WAT	432	25.178	20.516	50.622	1.00	25.50

ATOM	1366	OW	WAT	433	35.002	19.983	52.334	1.00	19.82
ATOM	1367	OW	WAT	434	34.135	43.191	44.812	1.00	32.07
ATOM	1368	OW	WAT	435	27.063	23.208	54.289	1.00	23.70
ATOM	1369	OW	WAT	436	34.312	17.824	19.412	1.00	39.43
ATOM	1370	OW	WAT	437	20.753	13.370	41.155	1.00	28.09
ATOM	1371	OW	WAT	438	19.252	35.279	59.477	1.00	29.78
ATOM	1372	OW	WAT	439	35.323	21.057	33.845	1.00	26.66
ATOM	1373	OW	WAT	440	21.925	16.767	45.856	1.00	27.17
ATOM	1374	OW	WAT	441	32.382	17.266	39.169	1.00	28.79
ATOM	1375	OW	WAT	442	15.598	41.632	31.052	1.00	27.73
ATOM	1376	OW	WAT	443	29.982	36.780	29.435	1.00	33.39
ATOM	1377	OW	WAT	444	31.371	31.251	61.561	1.00	38.29
ATOM	1378	OW	WAT	445	19.759	24.735	53.771	1.00	36.44
ATOM	1379	OW	WAT	446	22.480	15.079	42.820	1.00	17.58
ATOM	1380	OW	WAT	447	31.988	43.715	40.911	1.00	32.48
ATOM	1381	OW	WAT	448	17.935	35.854	26.456	1.00	28.58
ATOM	1382	OW	WAT	449	39.435	11.740	46.219	1.00	55.63
ATOM	1383	OW	WAT	450	16.672	41.095	41.485	1.00	31.86
ATOM	1384	OW	WAT	451	21.716	44.110	44.322	1.00	34.21
ATOM	1385	OW	WAT	452	18.308	15.003	40.442	1.00	46.38
ATOM	1386	OW	WAT	453	16.863	20.586	46.633	1.00	33.96
ATOM	1387	OW	WAT	454	31.944	31.457	24.450	1.00	42.18
ATOM	1388	OW	WAT	455	33.475	15.082	27.168	1.00	29.91
ATOM	1389	OW	WAT	456	36.543	15.370	34.224	1.00	60.74
ATOM	1390	OW	WAT	457	29.506	42.389	39.975	1.00	50.14
ATOM	1391	OW	WAT	458	20.388	16.126	25.860	1.00	53.32
ATOM	1392	OW	WAT	459	40.036	27.768	47.622	1.00	39.85
ATOM	1393	OW	WAT	460	32.383	15.687	41.430	1.00	39.50
ATOM	1394	OW	WAT	461	24.106	44.984	36.684	1.00	69.51
ATOM	1395	OW	WAT	462	22.963	42.283	26.675	1.00	42.87
ATOM	1396	OW	WAT	463	8.582	32.282	51.088	1.00	27.98
ATOM	1397	OW	WAT	464	23.257	19.528	23.889	1.00	34.76
ATOM	1398	OW	WAT	465	21.735	11.857	38.555	1.00	25.60
ATOM	1399	OW	WAT	466	27.314	36.489	57.830	1.00	58.08
ATOM	1400	OW	WAT	467	40.667	22.670	25.260	1.00	47.16
ATOM	1401	OW	WAT	468	10.401	39.140	49.837	1.00	41.30
ATOM	1402	OW	WAT	469	37.248	23.884	49.023	1.00	29.62
ATOM	1403	OW	WAT	470	21.277	40.716	54.364	1.00	33.13
ATOM	1404	OW	WAT	471	20.847	42.289	42.598	1.00	41.23
ATOM	1405	OW	WAT	472	33.078	36.978	29.346	1.00	29.31
ATOM	1406	OW	WAT	473	35.934	28.368	27.882	1.00	60.80
ATOM	1407	OW	WAT	474	38.008	24.709	46.253	1.00	34.90
ATOM	1408	OW	WAT	475	27.705	21.292	52.433	1.00	33.44
ATOM	1409	OW	WAT	476	37.983	27.433	50.682	1.00	30.01
ATOM	1410	OW	WAT	477	40.276	29.674	40.928	1.00	41.29
ATOM	1411	OW	WAT	478	39.094	29.615	52.097	1.00	30.12
ATOM	1412	OW	WAT	479	31.439	33.313	26.658	1.00	42.81
ATOM	1413	OW	WAT	480	10.829	39.751	38.732	1.00	44.07
ATOM	1414	OW	WAT	481	14.656	39.402	38.495	1.00	33.96
ATOM	1415	OW	WAT	482	34.006	14.898	31.399	1.00	51.26
ATOM	1416	OW	WAT	483	20.382	13.189	36.365	1.00	44.95

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What is claimed is:

1. A method of identifying a compound having atomic coordinates with non-trivial similarity to selected coordinates of atoms of a mammalian endostatin,  
5 comprising:
  - a) providing a library of atomic coordinates of compounds in a library of candidate compounds; and
  - b) comparing the library atomic coordinates  
10 to the selected coordinates of a mammalian endostatin; and
  - c) selecting from the library at least one candidate compound on the basis of selection criteria which include similarities between the atomic coordinates  
15 of the selected candidate compound and the atomic coordinates of the mammalian endostatin.
2. The method of claim 1 in which the coordinates of the mammalian endostatin comprise at least one pair of coordinates of Appendix A.
- 20 3. The method of claim 1 or claim 2 in which the mammalian endostatin is human endostatin.
4. The method of claim 2 in which the coordinates of mammalian endostatin include coordinates of atoms in a large basic structure area defining a  
25 heparin binding site.
5. The method of claim 1 in which coordinates of endostatin are stored in a computer-readable medium, and compared to coordinates of candidate compounds also stored in a computer-readable medium.

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6. The method of claim 1 or claim 5 in which at least one of the selected endostatin coordinates represents a coordinate of an atom involved in heparin binding.

5 7. The method of claim 1 or claim 5 in which at least one of the selected endostatin coordinates represents an atom of at least one of the following amino acid residues: Arg155; Arg158; Arg169; Arg 178; Arg184; Arg 193; Arg 194; Arg197; Arg259; and Arg270 of mouse  
10 endostatin.

8. The methdo of claim 1 or claim 5 in which at least one of the selected endostatin coordinates represents an atom of at least one of the following amino acid residues: Arg154, Arg157, Arg168, Arg177, Arg183,  
15 Arg192, Arg193, Arg 196, Arg258, Arg 259, and Arg 269 of human endostatin.

9. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of an amino acid involved in receptor binding.

20 10. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of an amino acid residue necessary for proteolytic cleavage.

11. The method of claim 1 in which at least one  
25 of the selected endostatin coordinates represents an atom of an amino acid residue exposed on  $\alpha$ -helix A.

12. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of Phe162 or Phe165 of mouse endostatin.

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13. The method of claim 1 in which at least one of the selected endostatin coordinates represents an atom of Phe161 or Phe164 of human endostatin.

14. The method of claim 1 in which at least one  
5 of the selected endostatin coordinates represents an atom of an amino acid residue involved in the endostatin fold related to the oligosaccharide binding site of E-selectin.

15. The method of claim 1 in which at least one  
10 of the selected endostatin coordinates represents an atom of one of the following amino acid residues: Glu267; Leu 284; Lys292; His297; Asn298; Tyr300 of mouse endostatin.

16. The method of claim 1 in which at least one  
15 of the selected endostatin coordinates represents an atom of one of the following amino acid residues: Glu266, Leu283, Ser291, His296, His297, and Tyr299 of human endostatin.

17. An anti-angiogenic fragment of endostatin comprising a domain selected from the group consisting of  
20 a heparin binding domain, a receptor binding domain, and exposed on  $\alpha$ -helix A domain, and a CRD domain.

18. A method of treating undesired angiogenesis by administering to a patient an anti-angiogenic amount of the fragment of claim 14 or of a compound identified  
25 by the method of claim 1.

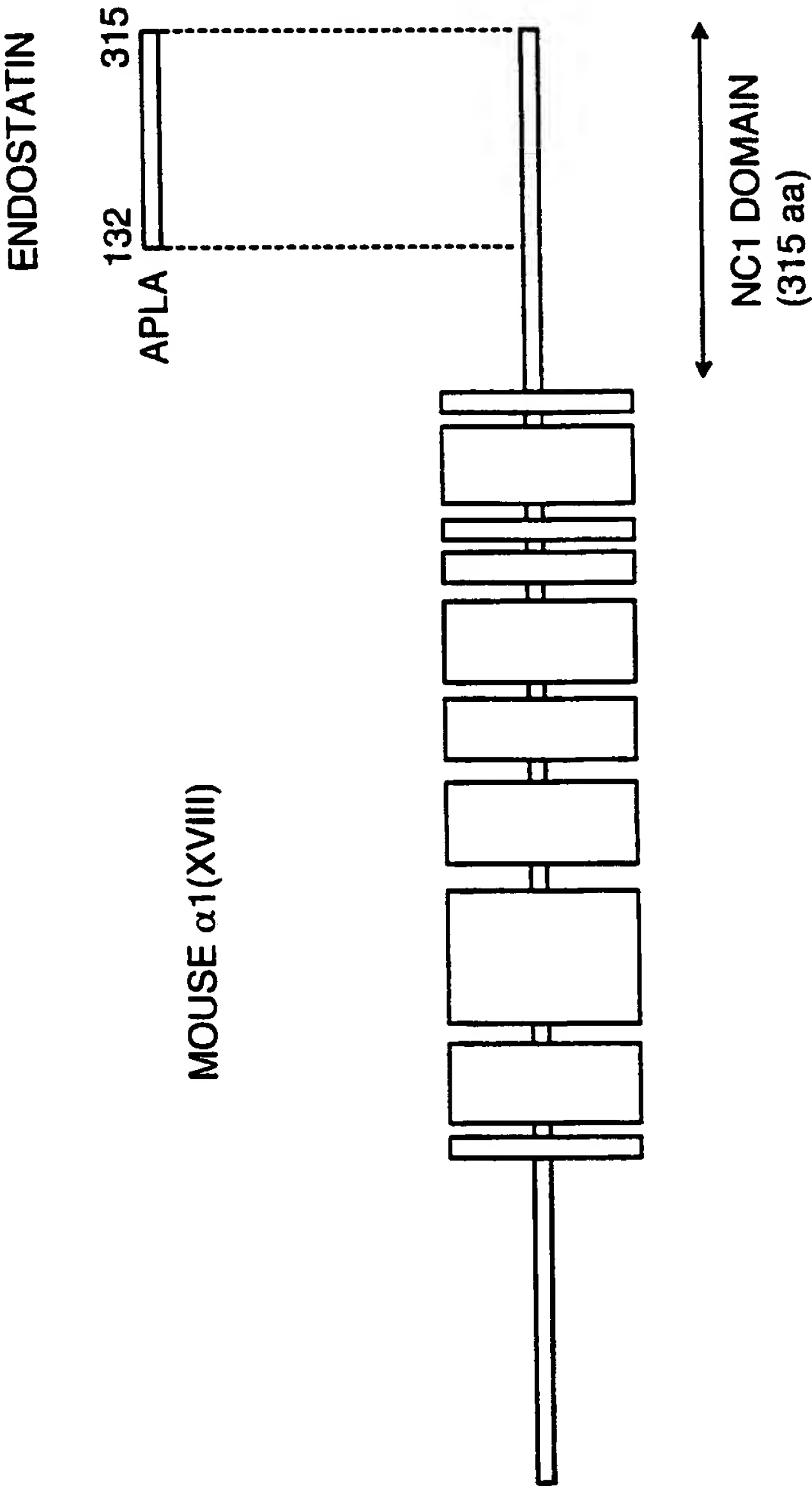


FIG. 1



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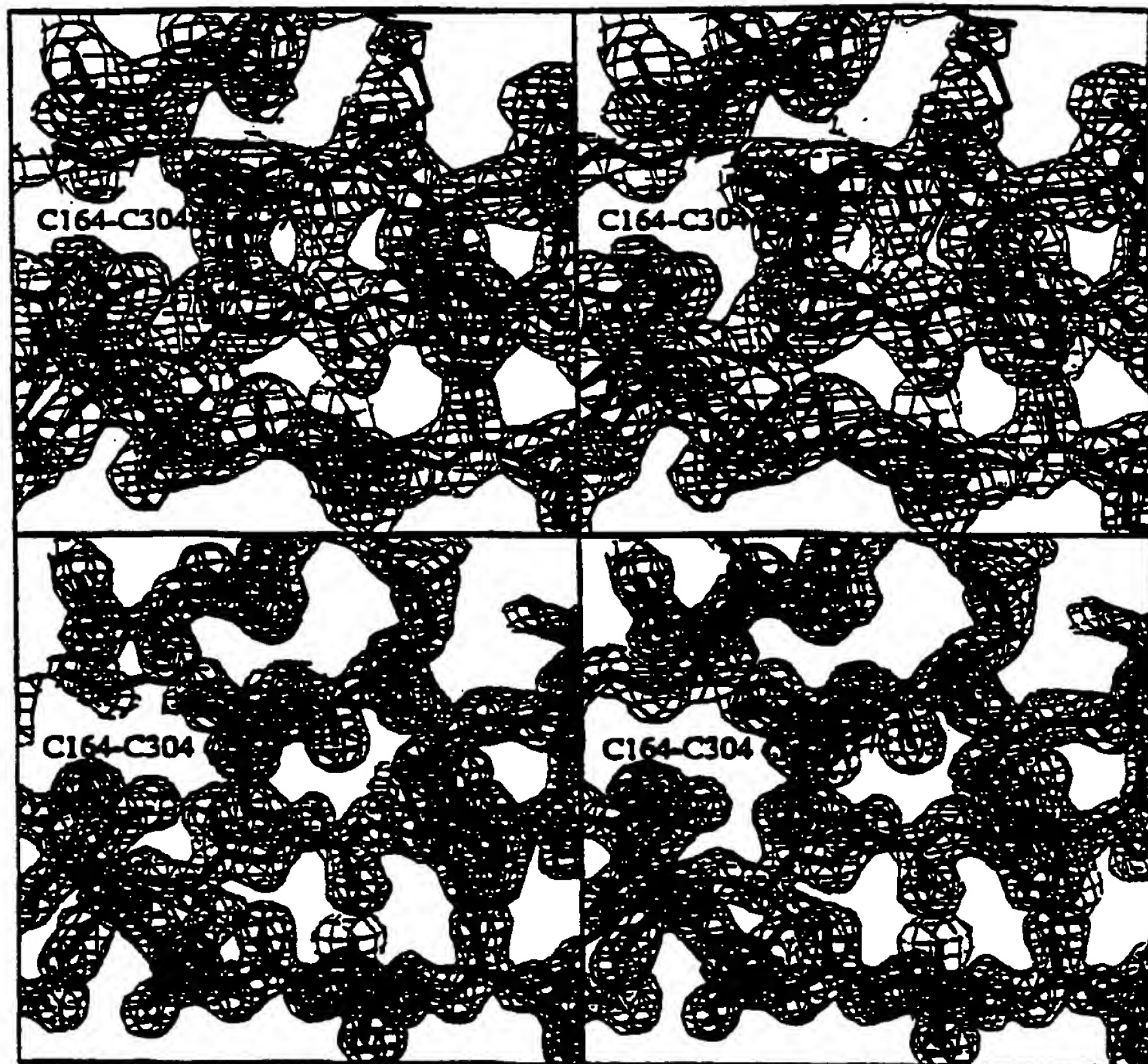


FIG. 2

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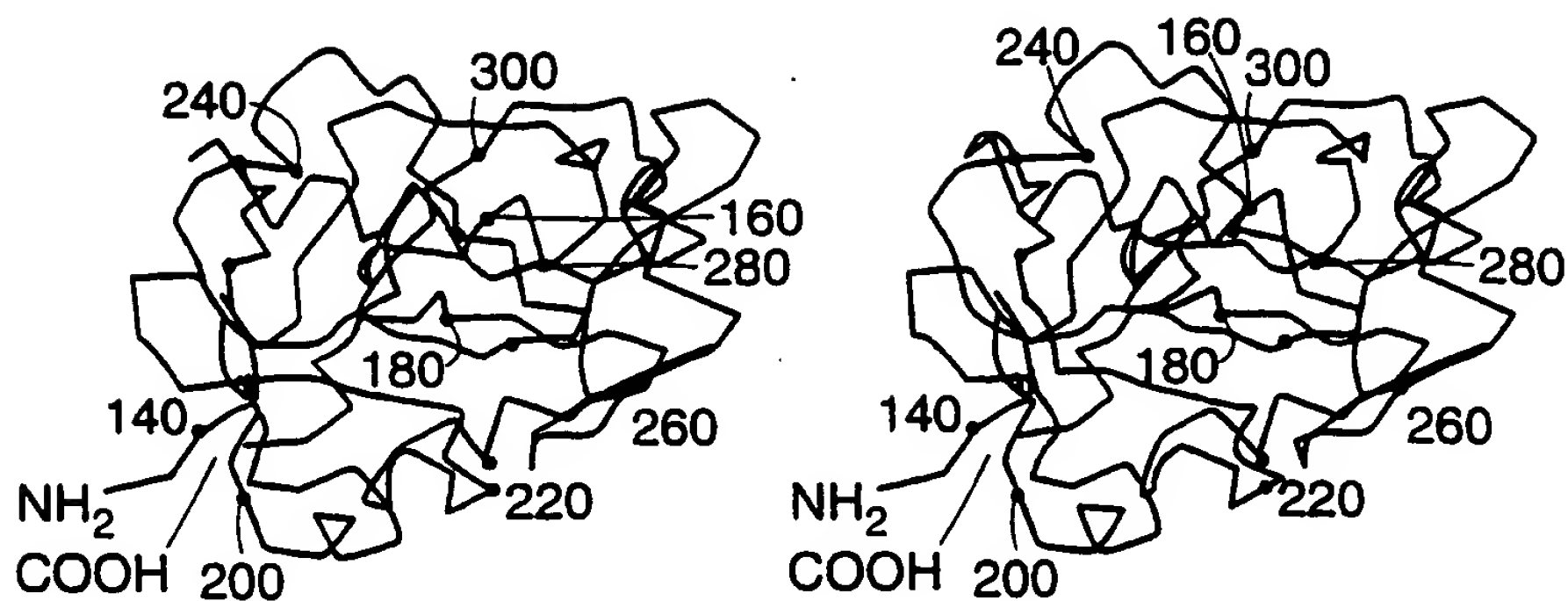


FIG. 3A

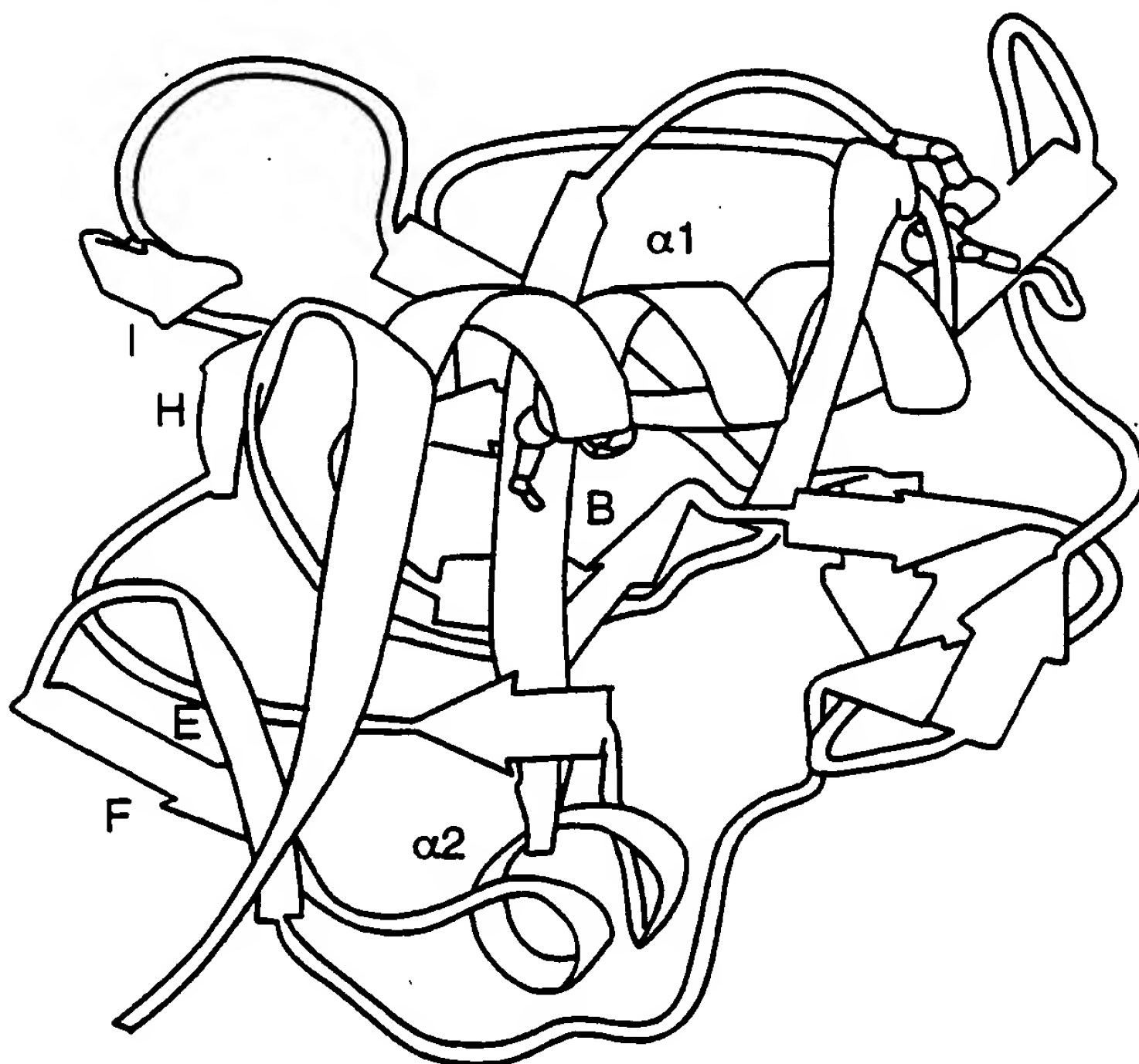


FIG. 3B

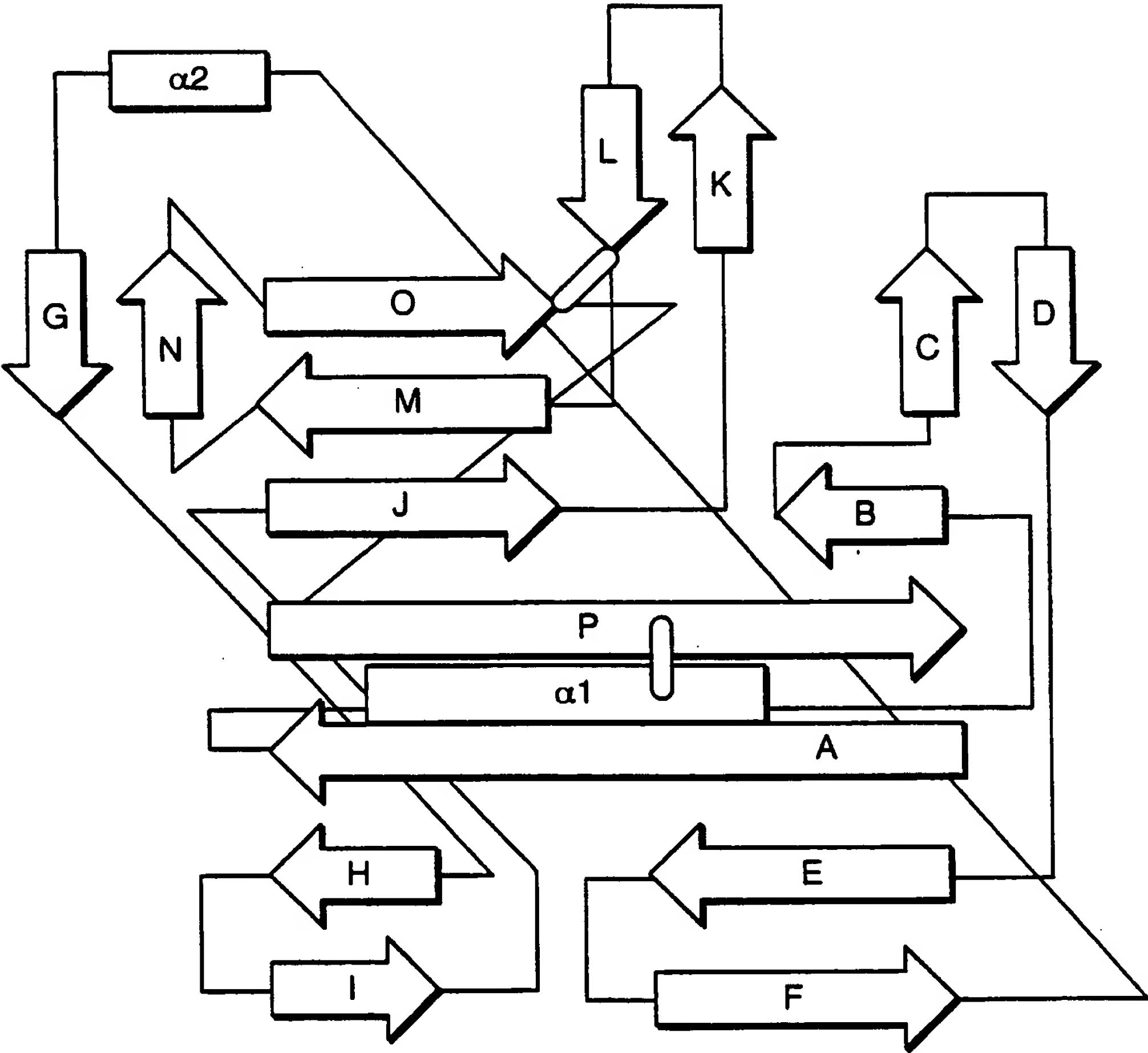


FIG. 3C

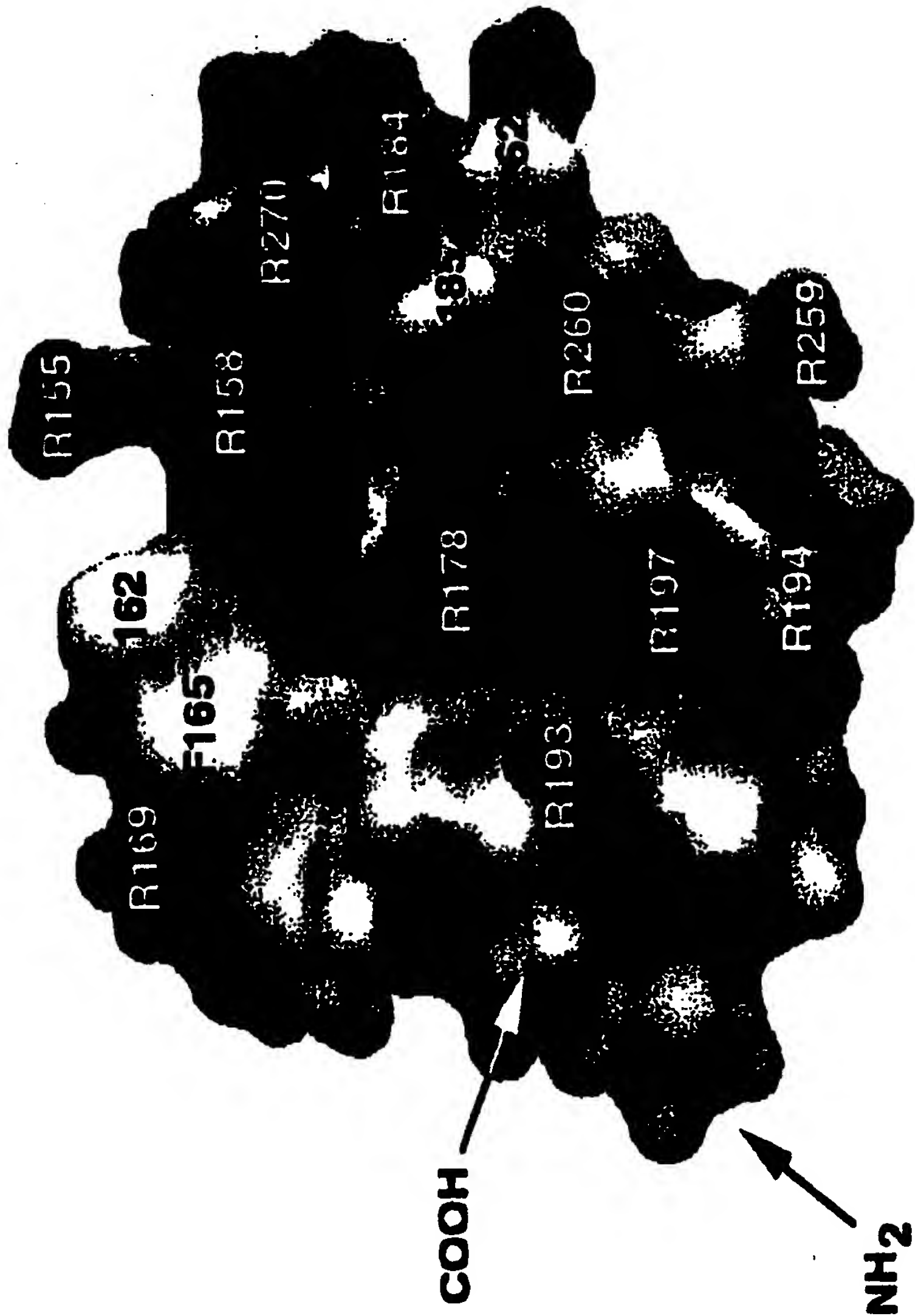


FIG. 4A

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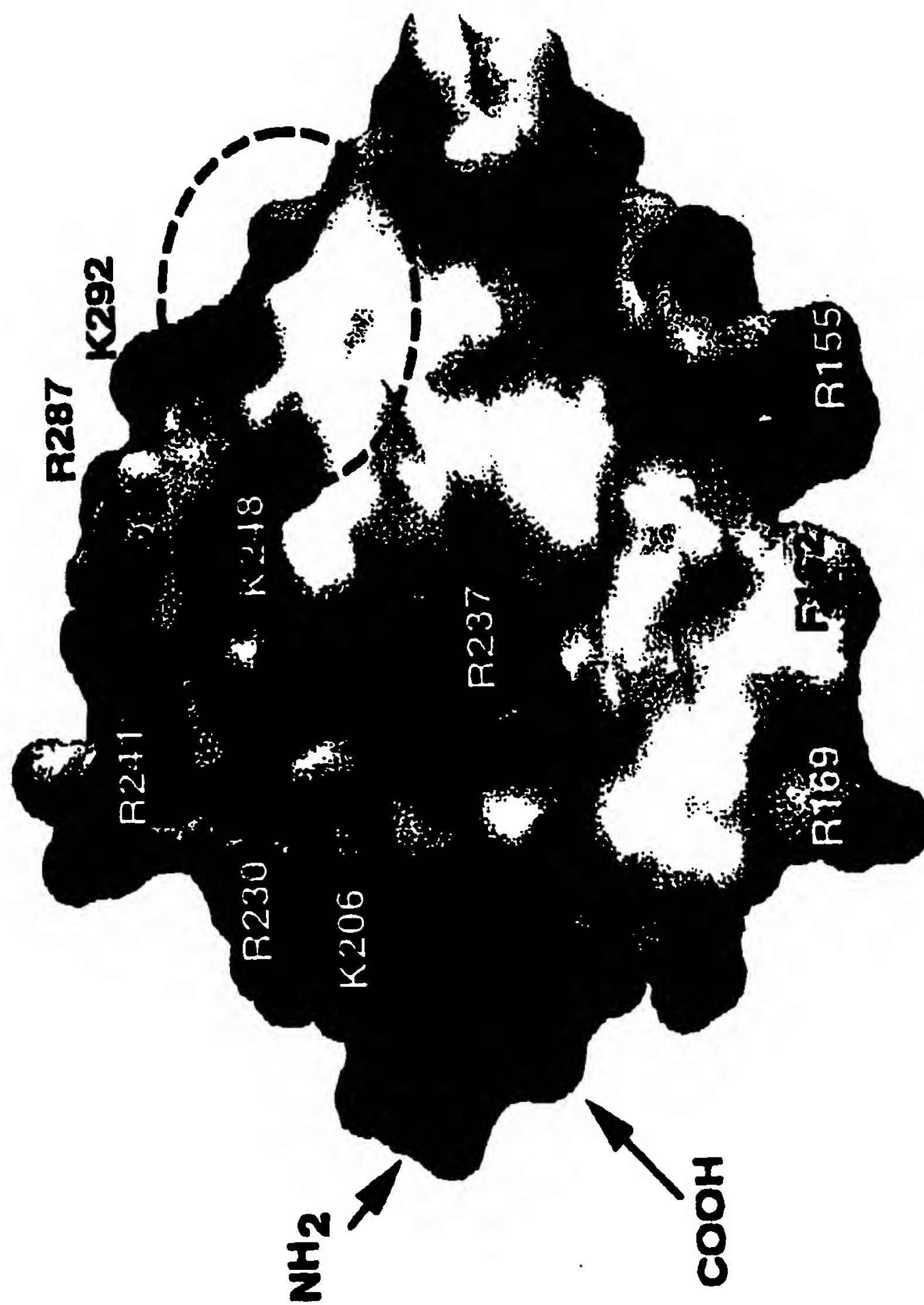


FIG. 4B

Human House	Human House	Human House	Human House	Human House	Human House	Human House	Human House
90	180	270	360	450	540	630	720
GGAGAGTTGGAGCAGATGGAAATCCCGGGTTCCCGGGCTCTCCGCGAGAGGGGCAATGCTGGGCGCCCAAGGGGCCAAAGGGAGACAGA G E V G A D G I P G P P G L P G R E G I A G P Q G P K G D R A Q I P P A	GGCAGCCCGGAGAGAGGGAGATCCAGGGAGGAGCTGGGCGAGCCCGGGCTCTCCGCGAGAGGGGCAATGCTGGGCGCCCAAGGGGCCAAAGGGAGACAGA G S R G E K Q D P G K D G L G Q P G L P G P R G P P G P V I H P N	TAGTGTGGAGCAGGAGCGGATCCGTCTGAGGCTCCCGGACCTGAGGGCCCGGGGTTTGGCAGGCTTTCCTCCCGACCTGCGAGGACCC Y V S E Q D G S V L S V P G P E G R R G F A G F P G P A G P S E K A I V T	AAGGGCAAGCTGGGCTCTAAGGGGGAAGTACCTCCCGGACCCAGGGTGAGAGGGTGACCGGGCAGCATCTTCAGCCCGACCGC K G N L G S K G E L G S P G P K G E K G E P G S I F S P D G D Q L	GGTGGCCCTGGCCCTGCCAGAGGAGCCAGGGAGAGCGGGCTTCGAGGACCCCGGGCTTATCGGACCGCGGGGTACAGGGA G A L G P A Q K G A K G E P G F R G P P G L Y G R P G Y K G R H P	GAGATTGGCTTCTGGAGCGCGGTGCGCCCGGATGAACGGATGAAGGAGAGGAGGAGCGGAGATGCCAGCCTTGATTT E I G F P G R P G R P G M N G L K G E K G E P G D A S L G F T	GGCATGAGGGGAATGCCCGGCCCCCAGGAGCTCCAGGCCCCCAGGCCCCCAAGGAGAGTGTGCTGAG G M R G M P G P P G P P G P P G P P G T P V Y D S N V F A E S L Q Q V H I A V	TCCAGCGCCCGGCTCCAGGATGCGAGGAGATCAGGGCTCCAGGAGCCAGGCCCCCAAGGAGAGTGGGCCCCCGGAGCCA S S R P G P P G L P G N Q G P P G P K G P K G E V G P P G P G L Q Q V S D
810							
CCAGGGCAGTTTGGCTTCTTCCAGAGGAGGCTGAATGAGGGGAGAGGAGAGCGAGTGTGATGTCAGGACAGAGGCGGA P G Q P P P D P L Q K E A E M K G E K G D R G D A G Q K G E I L F H L D							

(PRIOR ART)

**FIG. 5A**



	900	AAGGCGAAGCCGGGCGGCGGTTCCTTGCACCTGCCCGGGCGGCGCAGGCCCAAGCCACCTGGCTACCCTGGGATTCCA R G E P G G G Q F S L P G A P G A P G P R G Y P G I P
Human House	990	> GTCCAAAGGAGAGCATCCGGCGCACCCCGGCCACTGACCTCAGGACCCCCCGGCATGGCTACGAGGGCGCCAGGCCCT G P K G E S I R G Q P G P P G P Q G P P G I G Y E G R Q G P
Human House	1080	CCTGGCCCCAAGCCCCCAGGGCCCTTTCACTTCTTGCCCTCACAGCAGACTATCAAGGTTCCGGGCTCCGGCCCCCCCCTGG P G P P G P P G P P S F P G P H R Q T I S V P G P P G P P G
Human House	1170	CCCCCTGGGCCCTGAACCTAGGGGCTCTCTCAGCCAGGTAGGCTTCGGCTACAGGCCAGGCCATGCTGGGCCAGGTGCAGAG P P G P P G T M G A S S G Q V R L W A T R Q A M L G Q V H E
Human House	1260	GTTCCGAGGGCTGCTCATCTTGTGGCCGAGAGAGAGCTCTAGTCCCGGTGCAAGGGTTCCGAGGTTCCAGCTGAGGCC V P E G W L I F V A E Q Z E L Y V R V Q N G F R K V Q L E A
Human House	1350	CGAACACCACTCCACGAGGACGACATAAGTGGCCCTTGCAGCCCGTGTGCTGCAGCTGCAGACAGCAACCCCTACCGGG R T P L P R G T D N E V A A L Q P P V V Q L H D S N P Y P R
Human House	1440	CGGAGCACCCCCACCGCGGCTTGGGGCAGATGATCTCTGGCCAGCCCGCTGGGCTGCCGAGCCCCAGCCCTACCCC R E H P H P T A R P W R A D O I L A S P P G L P E P Q P Y P
Human House	1530	GAGGCCCCGACACAGCTCTAGTGCACCTGGGGCGGCGAGCCAGCCACCGCCACCGGAGCTTCACGCGGTG G P H H S S Y V H T C G P A R P T S P P A H S H R D F Q P V
Human House	1620	CTCCACCTGCTTGCCTCACAGCCCCCTGTGAGGGGCGATGGGGCGATCCGGGCGGCTTCCAGTGTTCAGCAGGGCGGGCC L H L V A L N S P L S G G M R G I R G A D F Q C F Q Q A R A
Human House	1710	GTGGGCTGGGGGACCTTCCGGGCTTCTGTCTGGCGCTGCAGGACCTGTACAGCATGTTGCCCGTCCGACGGGCGAGCGGTG V G L A G T F R A F L S S R L Q D L Y S I V R R A D R A A V

**(PRIOR ART)**  
**FIG. 5B**

**(PRIOR ART)**  
**FIG. 5C**

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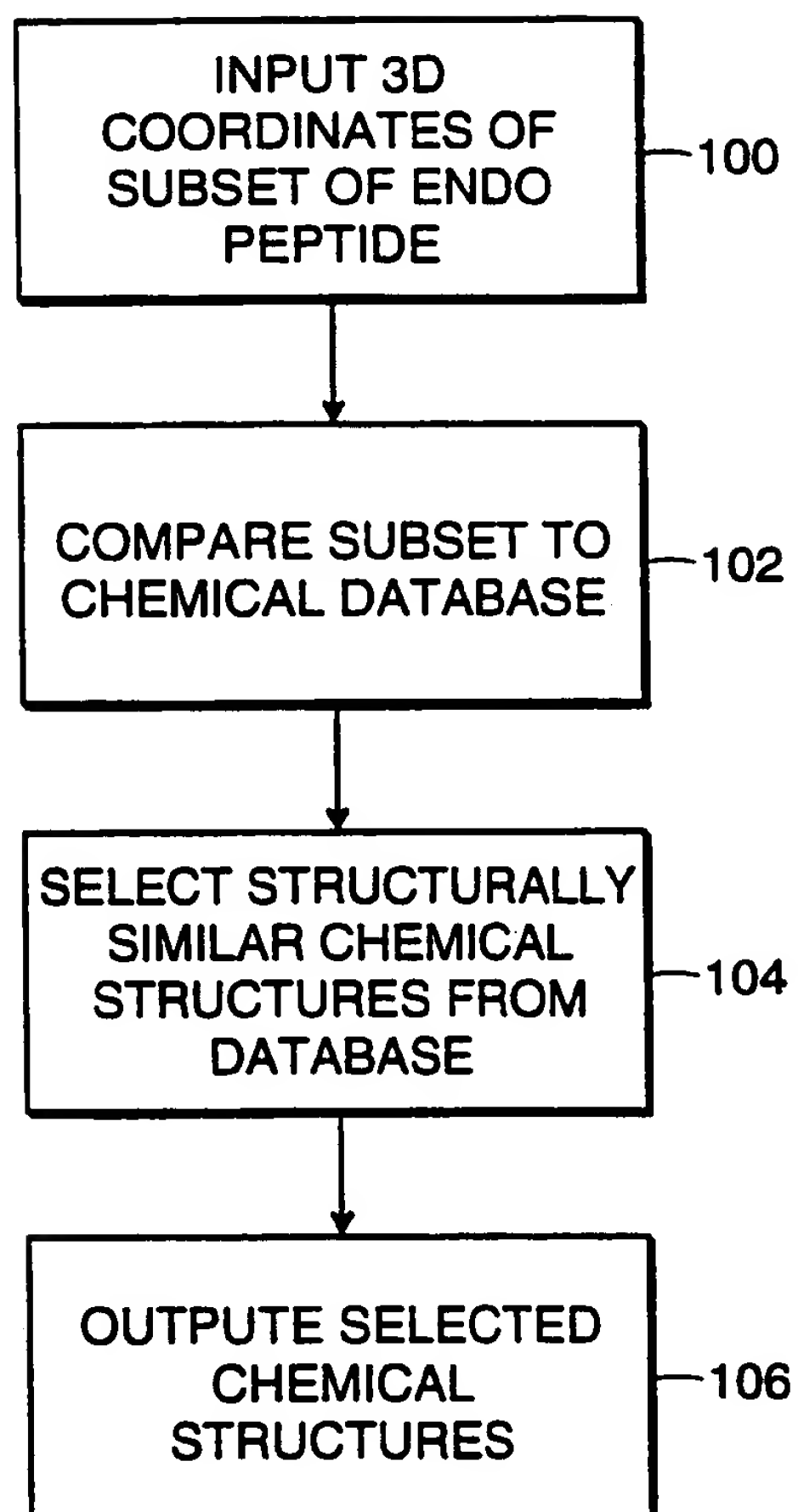


FIG. 6

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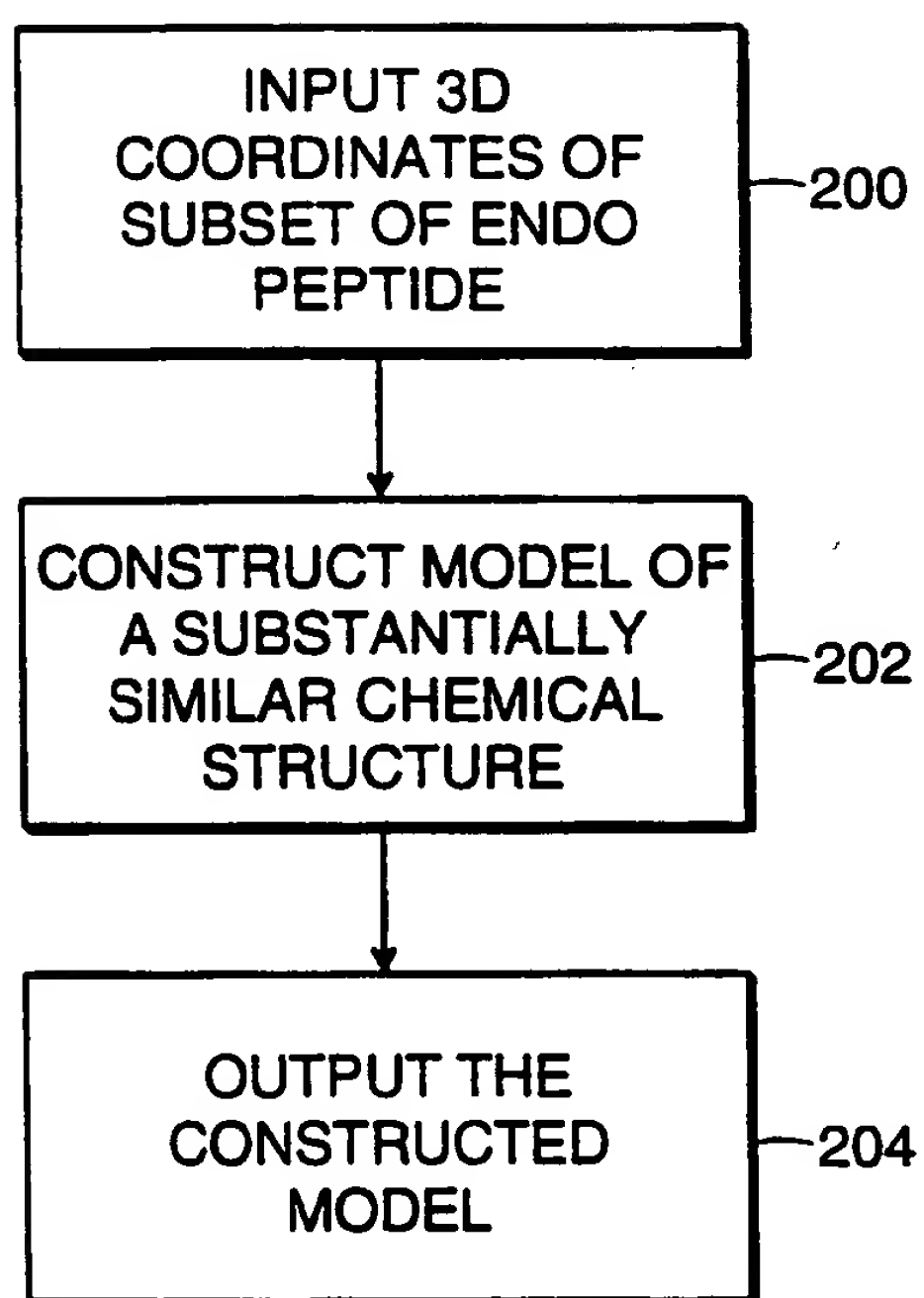


FIG. 7

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/26783

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : G06G 7/48; C07K 1/00, 14/00, 16/00, 17/00

US CL : 364/578; 530/300, 350, 356; 514/2

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 364/578; 530/300, 350, 356; 514/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS Dialog WEST (Derwent, USPAT, JPOABS EPOABS)  
endostatin, x-ray, crystal structure, atomic coordinates

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DING et al. Zinc-dependent dimers observed in crystals of human endostatin. Proc. Natl. Acad. Sci. 01 September 1998, Vol. 95, No. 18, pages 10443-10448, see entire document.	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

13 MARCH 1999

Date of mailing of the international search report

31.03.99

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